A.M.A.

American Journal OF DISEASES OF CHILDREN

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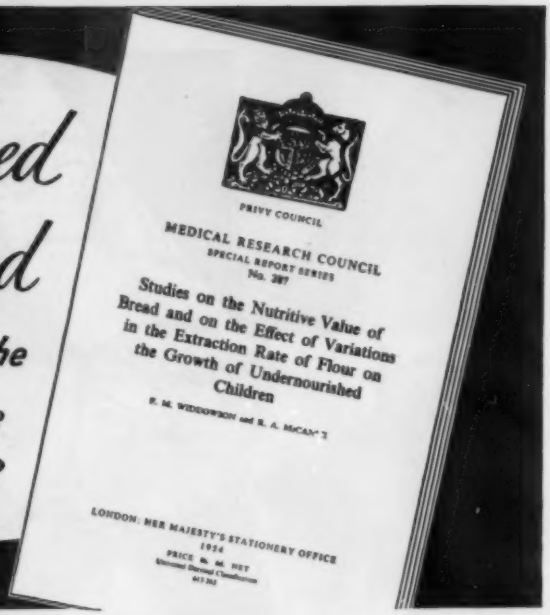
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*Widdowson, E. M., and McCance, R. A.: Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children, Medical Research Council, Special Report Series, No. 287, London, Her Majesty's Stationery Office, 1954.

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1. Ratner, B. et al: A.M.A. Am. J. Dis. Child. 89:187, 1955.
2. Glaser, J., and Johnstone, D. E.: J.A.M.A. 153:620, 1953.

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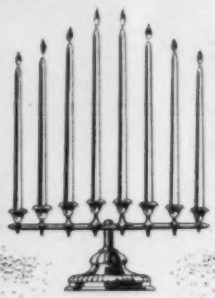

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1. Gatski, R.L.: Chlorpromazine in the Treatment of Emotionally Maladjusted Children–A Preliminary Report, J.A.M.A. *157*:1298 (April 9) 1955.
2. Flaherty, J.A., and Gatski, R.L.: Management and Rehabilitation of Emotionally Maladjusted Children–An Evaluation of Chlorpromazine ('Thorazine'), Presented as a scientific exhibit, 104th meeting of the American Medical Association, Atlantic City, New Jersey, June 6-10, 1955.
3. Sainz, A.A.: Clinical Applications of Chlorpromazine in Psychiatry, Presented before a joint session of the American Psychiatric Association and the Medical Science Section of the American Academy for the Advancement of Science, Berkeley, Calif., December 30, 1954.
4. Freed, H., and Peifer, C.A.: Treatment of Hyperkinetic Emotionally Disturbed Children with Prolonged Administration of Chlorpromazine, Presented before the American Psychiatric Association, Atlantic City, New Jersey, May 11, 1955.
5. Freedman, A.M.; Effron, A.S., and Bender, L.: Pharmacotherapy in Children with Psychiatric Illness, Presented at the meeting of the Society of Biological Psychiatry, Chicago, Ill., June 11-12, 1955.
6. Rees, E.L.: Preliminary Case Report of the Use of Chlorpromazine Hydrochloride ('Thorazine') S.K.F. in Emotionally Disturbed Children, in press.

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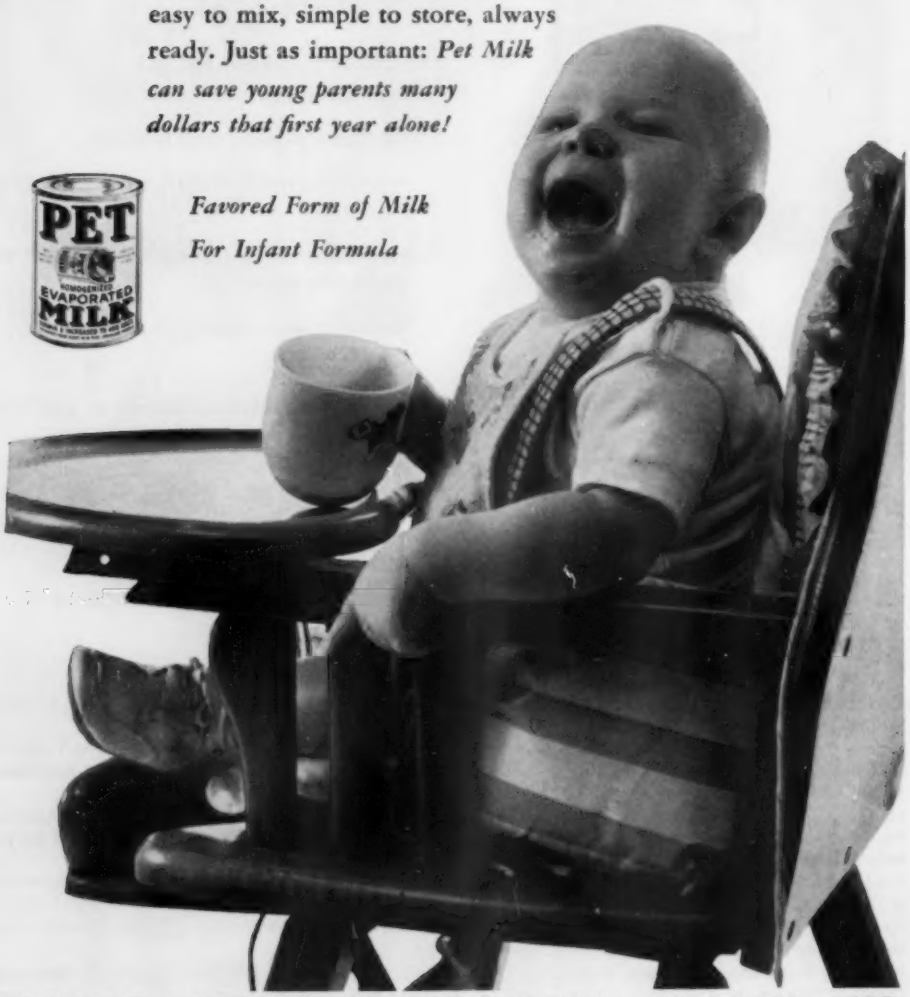

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A.M.A. American Journal OF DISEASES of CHILDREN

Serum Calcium and Phosphorus in Premature and Full-Term Infants

A Longitudinal Study in the First Three Weeks of Life

ERIKA BRUCK, M.D.
and
DAVID H. WEINTRAUB, M.D., Buffalo

Hypocalcemia with or without tetanic symptoms has frequently been observed in sick infants. This is particularly common during the first month of life.* In addition, tetany of the newborn occurs in infants who are not otherwise ill. These cases often present difficult etiologic and therapeutic problems. When many serum calcium determinations are done on young infants, frequent cases of hypocalcemia are discovered. An impression was gained that newborn infants who are premature or ill with any serious disease tend to have hypocalcemia, not necessarily associated with symptoms of tetany. The following questions therefore arose:

1. What are the "normal" fluctuations or variations of the serum calcium level in full-term and premature infants during the neonatal period?

2. Which factors influence the serum calcium level?

3. Can the symptomatology of the infants be correlated with the serum calcium level, considering also such other influences as the serum potassium level and the pH?

There is a large literature on the so-called normal calcium level in full-term normal infants.† Less is known about serum calcium levels in premature infants.[7] Longitudinal studies on the course of the serum calcium level in the individual newborn infant, are reported only by Graham, Barness, and György[9] and by Todd, Chuinard, and Wood.[5]

It was the purpose of the present study to elucidate some of the unsolved problems which are indicated in the questions. The following influences on serum calcium level were considered: parathyroid insufficiency, which has been suggested by Bakwin and others ‡; the serum phosphorus level, which in turn might be influenced by parathyroid activity or diet or other factors §; fasting and various diets; rate of growth; vitamin D deficiency; acidosis.[10]

CASE MATERIAL

A study was made of 51 premature and 21 full-term newborn infants. The premature infants were housed in the premature unit of the Children's Hospital and maintained so as to comply with conditions recommended by the Committee on Fetus and Newborn of the American Academy of Pediatrics.[14] Specially trained nurses made accu-

Submitted for publication Sept. 6, 1955.

From the Statler Research Laboratories of The Children's Hospital of Buffalo and the Department of Pediatrics, The University of Buffalo School of Medicine.

* References 1 and 2. Bruck, E., and Maitland, B.: Hypocalcemia, Exhibit at National Convention of the American Academy of Pediatrics, Atlantic City, N. J., November, 1948.

† References 2-8.

‡ References 3 and 10-12.

§ References 10-12.

TABLE 1.—*Feeding of Infants During the Study Period* *

	No. of Premature Infants	No. of Full-Term Infants
Alacta † formula (0.8 Cal./cc., Ca:P ratio 1.2)	27	..
Evaporated milk formula (0.7 Cal./cc., 10% carbohydrate)	3	..
Whole cow's-milk formula	..	6
Human milk	9	5
Mixed or alternating human and cow's milk	8	4
No feedings	4	6

* Alacta is a proprietary powdered half-skimmed cow's-milk preparation.

† The Alacta formula contained 0.22% of calcium and 0.19% of phosphorus.

rate observations of symptoms, which were checked by one or both of the authors. Accurate records of daily weight and food and fluid intake were kept. Feeding regimens are recorded in Table 1. All premature infants received vitamin D in the form of calciferol (Drisdol), 1250 units a day, and 50 mg. of ascorbic acid, starting on the eighth day of life.

The full-term infants were housed in the newborn nurseries of the maternity division of the Children's Hospital. Observations of symptoms, food intake, and daily weight were recorded. These infants were not under as close observation as those in the premature unit, and occasional symptoms may have been overlooked. The full-term infants did not receive vitamin supplements, with the exception of one ill infant. Feeding regimens are recorded in Table 1.

Six infants were sick during the study period. Details of their course are described in the Appendix. All other infants in this study were "well" premature and full-term infants. They were unselected.

METHODS OF STUDY

Samples of venous blood were taken before the first feeding and at intervals during the first three weeks of life. In 41 cases cord blood was also examined. The blood was collected under liquid petrolatum and examined shortly after clotting for CO_2 content and pH. Thereafter the serum was separated from the clot and calcium, phosphorus, phosphatase, and potassium were determined.

The pH was measured with the micro McInnes glass electrode of a Cambridge Instrument Company potentiometer, CO_2 with a standard Van Slyke manometric method, calcium was determined with the micromethod of Sobel and Sobel,[15] inorganic phosphorus by the Gomori modification of the Fiske and Subbarow method[16] and phosphatase by the Bodansky procedure[17]; potassium was measured with a Perkin-Elmer flame photometer with an internal lithium standard.

TABLE 2.—*Statistical Data for Serum Levels of Calcium, Inorganic Phosphorus, Phosphatase, and Potassium in Premature and Full-Term Infants and in Umbilical Cord Blood*

	Premature Infants	Full-Term Infants	Significance of the Difference of Means P	Cord Blood
Calcium, mg./100 cc.				
Number of patients	51	21	..	41
Number of determinations	154	43	..	41
Mean of all determinations ± S. E. of the mean	8.27 ± 0.105	9.06 ± 0.122	< 0.002	10.59 ± 0.185
S. D.	1.31	0.796	..	1.186
Mean of average of each * patient ± S. E. of mean	8.31 ± 0.123	..	..	..
S. D.	0.88	..	..	..
Mean of lowest value of each patient ± S. E. of mean	7.44 ± 0.167	8.87 ± 0.186	< 0.002	..
S. D.	1.19	0.85	..	..
Inorganic phosphorus, mg./100 cc.				
Number of patients	51	20	..	37
Number of determinations	145	39	..	37†
Mean of all determinations ± S. E. of the mean	7.73 ± 0.145	7.49 ± 0.282	< 0.5	6.62 ± 0.196†
S. D.	1.74	1.76	..	1.191
Mean of highest value of each patient ± S. E. of mean	8.70 ± 0.200	8.35 ± 0.376	< 0.5	..
S. D.	1.43	1.68	..	..
Phosphatase, B. U.				
Number of patients	44	17	..	..
Number of determinations	116	26	..	..
Mean of all determinations ± S. E. of the mean	6.72 ± 0.250	4.55 ± 0.271	< 0.002	..
S. D.	2.69	1.38	..	..
Potassium, mEq./L.				
Number of patients	34	18	..	..
Number of determinations	86	27	..	..
Mean of all determinations ± S. E. of the mean	5.12 ± 0.065	4.48 ± 0.115	< 0.002	..
S. D.	0.89	0.60	..	..

* In this calculation only the mean value of several determinations on each individual was used for calculating the mean, S. D., and S. E. of the mean. This method may give a falsely high mean because the infants were often followed until the serum calcium became normal. But taking each level of every infant might give a falsely low mean because infants with low levels had more samples taken than those with more nearly normal levels.

† Omitting 2 values of 24.8 and 26.6 mg./100 cc., respectively. The next highest value was 9.1 mg./100 cc.

RESULTS

The results of the chemical analyses and statistical values are summarized in Table 2.

Calcium in Premature Versus Full-Term Infants.—It is seen that premature infants have a significantly lower and more variable serum calcium level during the newborn period than full-term infants. Both the average level and the lowest level reached by each infant during the observation period are lower in the premature infants.

The statistical mean of all determinations on all infants throughout the entire course of observation appears less revealing than the course of the calcium level in individual infants.

Figure 1 portrays the distribution of minimum calcium levels attained by each individual infant, differentiated as to the diet the infants received at the time the minimum level was reached. Again it is evident that there is a striking difference between the full-term and premature infants. Only two of the full-term infants ever had calcium levels below 8 mg. per 100 cc. and both of these were considered as "sick" infants. The mode of the minimum calcium level reached in this group was between 9 and 10 mg. per 100 cc. By contrast, 34 out of 51 premature infants reached levels below 8 mg. per 100 cc., and the mode was between 6 and 7 mg.

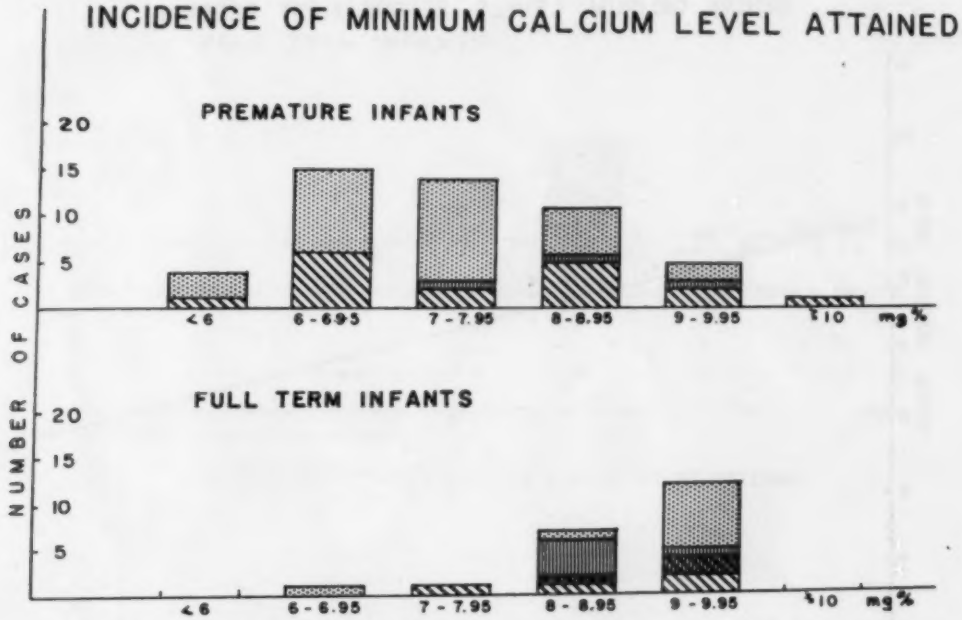


Fig. 1.—Incidence of minimum calcium level attained. Each infant is plotted as one unit in the ordinate for the various ranges of calcium levels, which are indicated, in milligrams per 100 cc. at the bottom of each column. Infants who had never received food before the minimum level was observed are represented by the dotted pattern, infants who were receiving cow's-milk formulas at the time of the minimum calcium level, by the diagonal stripes, and those receiving human milk, by vertical stripes.

Cord Blood.—The calcium and phosphorus levels of the cord blood showed no relation to the subsequent calcium levels in the infant. The lowest cord blood calcium level encountered was 6.35 mg. per 100 cc. in one infant, the next lowest was 8.95 mg. In every individual case the first calcium level taken in the infant was lower than that in the cord blood (0.8-4.6 mg. per 100 cc. fall in the first 24 hours).

Fasting.—It is seen in Figure 1 that the majority of infants reached their lowest level during the immediate postnatal fasting period.

In Figure 2 the fasting calcium levels are plotted against the infants' age at the time the blood sample was taken. In general, the longer the fasting period was extended, the lower was the calcium level. There was a significant correlation. After 33 or more hours no calcium level above 8 mg. per 100 cc. was observed, whereas all levels taken during the first 12 hours of life were above 8 mg.

Phosphorus in Premature and Full-Term Infants.—In the level of inorganic phosphorus, there was no significant difference between full-term and premature infants (Table 2).

Figure 3 shows the distribution of the maximum phosphorus level attained to be similar in full-term and premature infants. Before any feedings had been taken, the maximum phosphate levels were between 3.1 and 10.8 mg. per 100 cc.

During the first 36 hours of fasting (Fig. 4) there was no evident trend for the phosphorus levels to rise or fall; but the seven levels taken after more than 36 hours of fasting ranged from 7.9 to 9.7 mg. per 100 cc.

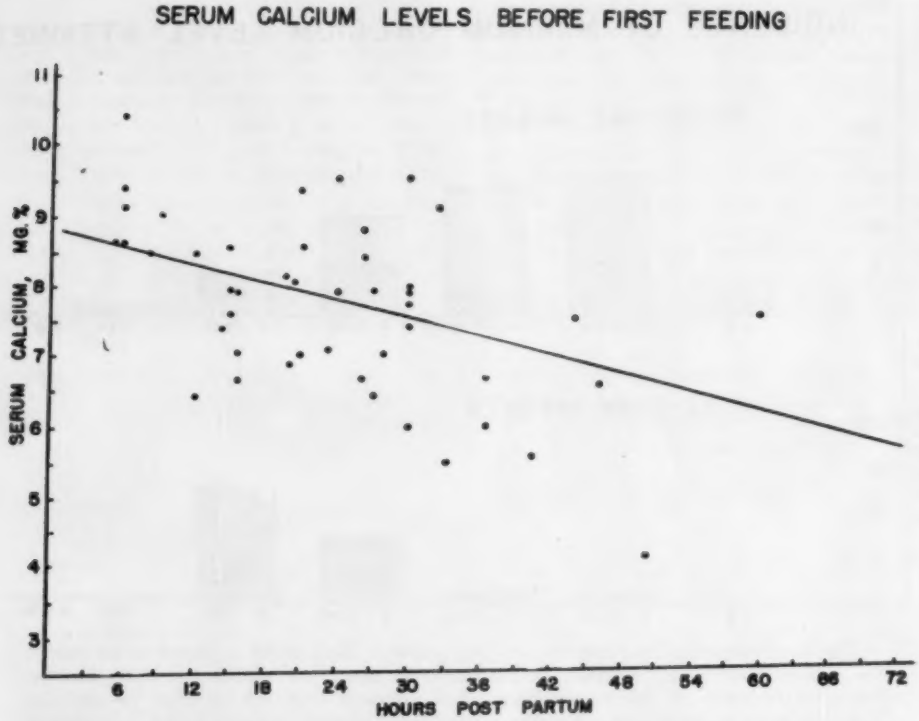


Fig. 2.—Serum calcium levels observed before the first feeding, plotted against the baby's age at the time of sampling. The correlation factor is $r = -0.480$ with S. D. 0.112. The regression equation, represented by the line, is $y = 8.82 - 0.0422\,x$, where y = serum calcium level and x = age in hours. The relationship would probably be represented more accurately by a curve than by a straight line.

Trends of Simultaneously Observed Courses of Calcium and Phosphorus Levels.—In order to correlate the trend of the calcium levels with the trend of the simultaneously obtained phosphorus levels, the fall or rise of both levels in 111 intervals between blood samples was recorded in Table 3. In 76 of the periods the calcium

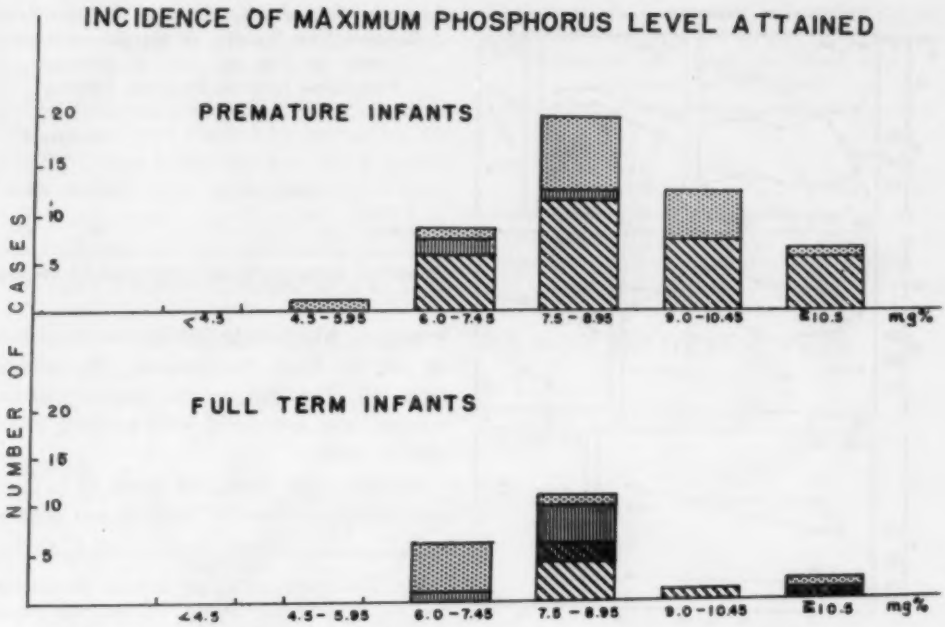
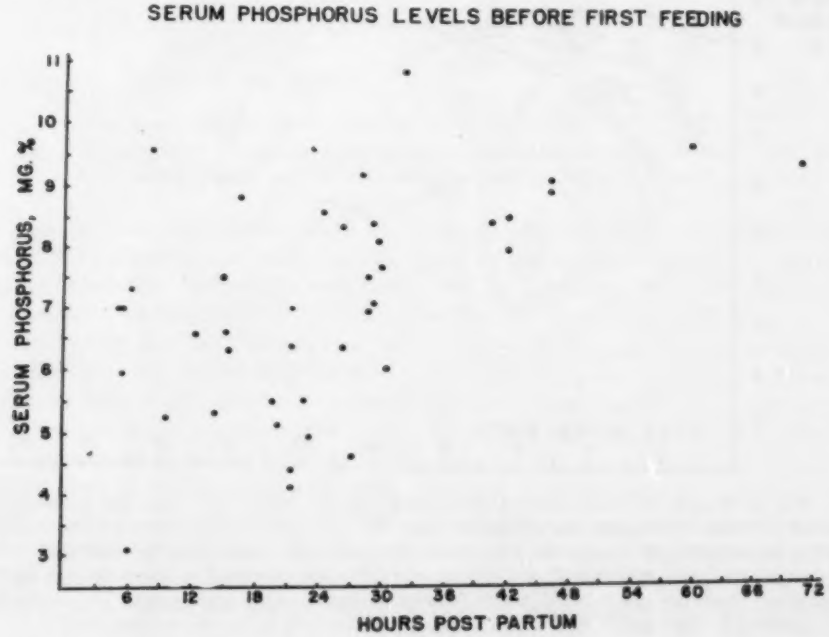


Fig. 3.—Incidence of maximum inorganic phosphorus level attained. The Figure is arranged like Figure 1.

Fig. 4.—Serum inorganic phosphorus levels observed before the first feeding, plotted against the baby's age at the time of sampling.



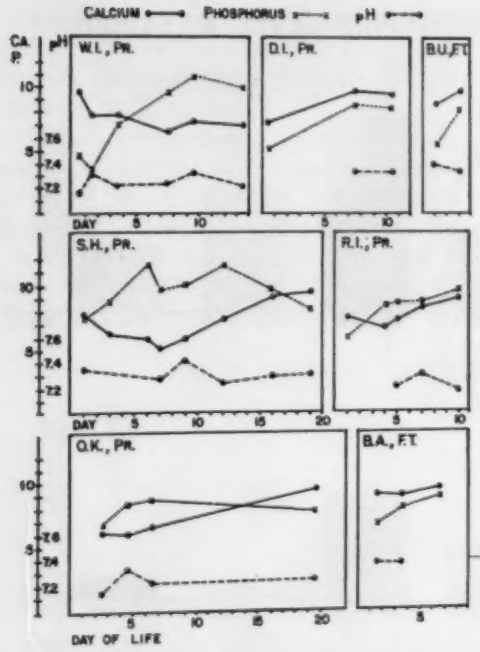


Fig. 5.—Course of serum calcium, phosphorus, and pH in individual infants. Pr. indicates premature, F. T., full-term infant.

TABLE 3.—*Fall or Rise of Serum Calcium Level Between Two Samples in the Same Infant Related to Fall or Rise of Inorganic Phosphorus Level in the Same Samples**

Calcium Level	Phosphate Level	
	Falling	Rising
Falling	8	27
Rising	38	38

* Intervals during which the level changed by less than 0.1 mg./100 cc. are omitted; $\chi^2 = 7.26$, $P = < 0.01$.

level rose, whether the phosphorus level rose or fell. In 35 of the intervals, the calcium level fell. This fall, in the majority of instances, was associated with a rising phosphorus level.

In individual cases, the levels of calcium and phosphorus are as likely to run parallel

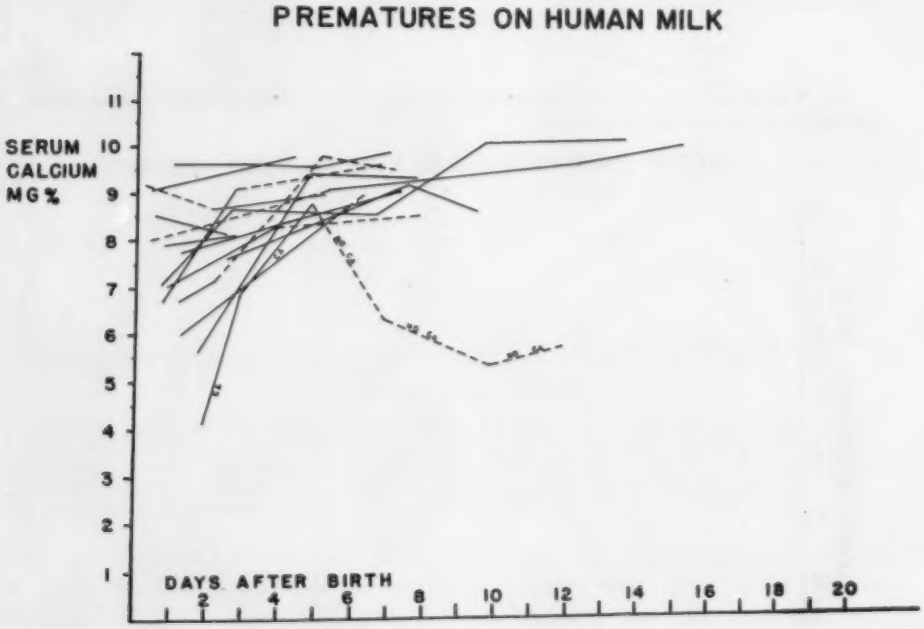


Fig. 6.—Course of serum calcium levels in premature infants who were fed human milk. In some infants, the feeding was changed at some time; the periods when infants received cow's milk are indicated by dashes, the times when they received human milk, by solid lines. One infant received both human milk and calcium gluconate from the third to the sixth days of life, inclusive; thereafter she received Alacta formula without calcium supplements. The medication is indicated by the signs "CA," "NO CA," along the course of her serum calcium level.

as in opposite direction; this fact is illustrated in Figure 5, in which the complete course in seven individual cases is charted.

Effect of Diet on Calcium Level.—The effect of diet was studied by comparing the serum calcium levels obtained while infants received cow's milk or human milk. Figure 1 indicates that in the majority of infants, the minimum calcium level was observed before any feedings had been given. With

TABLE 4.—*Fall or Rise of Serum Calcium Level Between Two Samples in the Same Infant Related to the Food the Infant was Receiving at the Time**

Feeding	Calcium Level	
	Falling	Rising
Cow's milk	28	52
Human milk	5	25

* $\chi^2 = 3.5$, $P = > 0.05, < 0.10$.

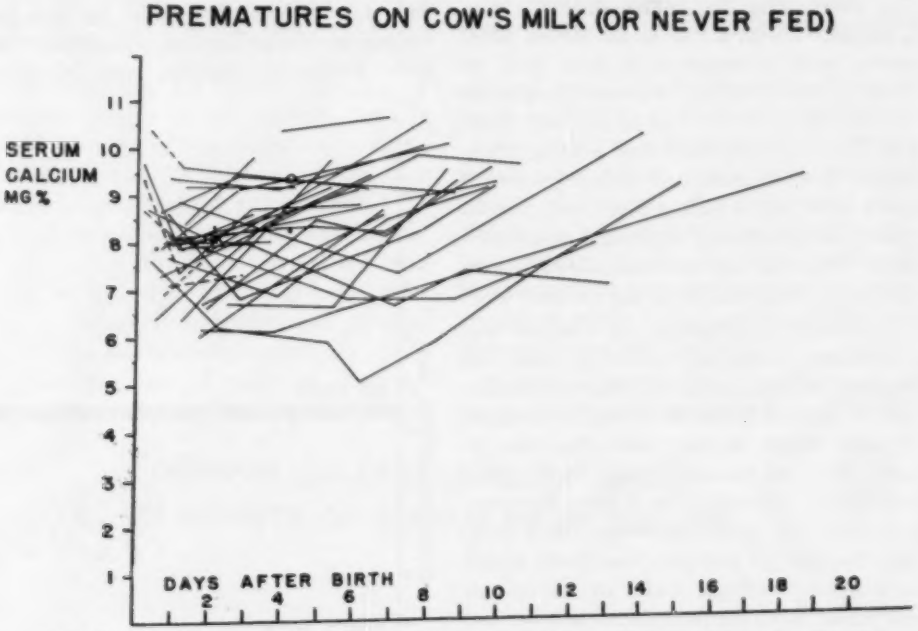


Fig. 7.—Course of serum calcium levels in premature infants who were fed cow's milk. The dashes indicate periods without any feedings, the solid lines periods of cow's-milk ingestion.

either type of food, the calcium level appeared to rise. When human milk was fed, the calcium level rose consistently with one single exception, as illustrated in Figure 6. When cow's milk was fed, calcium rose in 60% of the cases and fell in 40% initially. However, in almost all cases, the calcium level later on rose spontaneously and reached approximately normal levels by the end of the first or second week of life, as shown in Figure 7. This relationship is further illustrated in Table 4, in which the rise or fall of serum calcium level between any two samples is related to the type of feeding ingested during that period. The statement that the serum calcium level rises with human milk feedings and falls with cow's milk [12] is thus not consistently confirmed.

Effect of Diet on Phosphorus Level.—It was attempted to determine whether the different kinds of milk had an indirect influence upon the calcium level by influencing primarily the phosphorus levels. From Figure 3 it is evident that the maximum phosphorus level of individual infants was most frequently attained when they received cow's milk feeding, whereas the lowest calcium level, as mentioned above, was usually ob-

TABLE 5.—*Fall or Rise of Serum Inorganic Phosphorus Level Between Two Samples in the Same Infant Related to the Food the Infant Was Receiving at the Time**

Feeding	Phosphorus Level	
	Falling	Rising
Cow's milk	26	49
Human milk	20	14

* $\chi^2 = 5.6$, $P = < 0.02$.

served before any feedings had been given. The observation that intake of cow's milk is associated with a rise in the serum phosphorus level is confirmed in these data. In Table 5, the rise or fall of serum phosphorus level is related to the type of feeding. From this Table it is apparent that a rising phosphorus level is associated with ingestion of cow's milk and a falling level with human milk in a statistically significant number of cases. This rise was not necessarily associated with a depression of the calcium level.

Combined Observations of Calcium and Phosphorus Levels in Relation to Diet.—In Figure 8, all simultaneously observed calcium and phosphorus levels are plotted for samples obtained before feeding, and when the infants were fed human milk or cow's milk, respectively. On inspection of these diagrams, it appears that in the babies fed cow's milk, both the calcium and phosphorus are higher than before feedings, while in the infants fed human milk, the phosphorus is lower and calcium higher than in both other groups. This impression is confirmed in statistical evaluation (Table 6). All the differences between the means are statistically significant except for the difference between phosphorus levels of fasting babies and those fed human milk. It is evident that the scatter is extremely wide and that the correlation between simultaneous calcium and phosphorus levels is not consistent.

Effect of Growth.—The lower the birth weight or the greater the growth rate the greater should be the rate of deposition of calcium salts in the bones. From Stearns' data [18] it may be calculated that during the last month of pregnancy, 200 mg. of calcium is deposited in the bones of the fetus per day; according to the data collected by Hamilton and Moriarty [19] and by Givens and Macy [20] from the older literature, this figure would be closer to 300 mg. per day. Therefore, a prematurely born infant has a great deficiency of calcium in the bones, and one may assume a marked tendency for calcium to be withdrawn from the serum and deposited in the bones. Actually, the total amount of calcium available in the infant's serum is only a small fraction of the amount deposited daily for bone calcification at the rate prevailing in utero. Further, Hamilton,[21] and later Benjamin, Gordon, and Marples,[22]

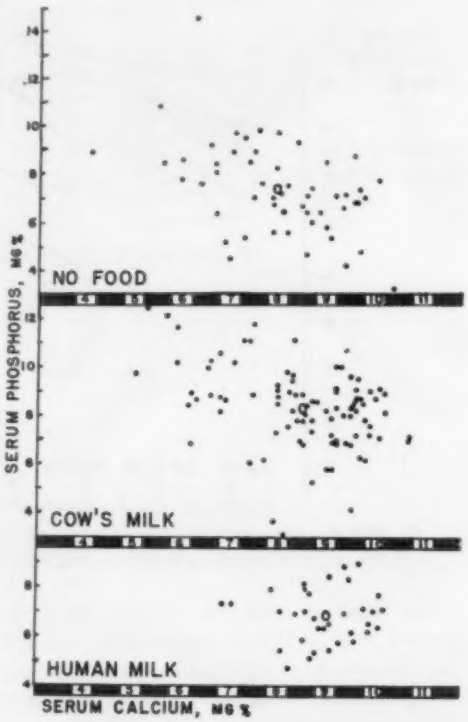


Fig. 8.—Simultaneously occurring serum levels of calcium and inorganic phosphorus in all infants, grouped according to the food the infant was receiving at the time. Each blood sample is represented as one dot. For the upper diagram (no feeding), the correlation factor between calcium *(x)* and phosphorus *(y)* is $r = -0.484$; S. D., $r = 0.104$, and the regression equation is $y = 12.767 - 0.687\,x$. For the middle diagram (cow's milk) $r = -0.392$; S. D., $r = 0.088$, regression equation: $y = 12.580 - 0.508\,x$. For the lower diagram, no significant correlation can be calculated. For the whole series, $r = -0.328$; S. D., $r = 0.066$; regression equation: $y = 11.431 - 0.442x$.

TABLE 6.—*Statistical Data for Serum Calcium and Inorganic Phosphorus Level in All Infants on Different Feedings*

	A No Food	B Cow's Milk	C Human Milk	Significance of the Difference of Means P B-A	C-A	C-B
No. of patients	54	46	20	..	..	..
No. of determinations	59	98	34	..	..	..
Calcium mean ± S. E. of the mean	7.99 ± 0.160	8.49 ± 0.124	8.99 ± 0.139	< 0.05	< 0.002	< 0.01
S. D.	1.22	1.30	0.814	..	..	..
Phosphorus mean ± S. E. of the mean	7.29 ± 0.255	8.27 ± 0.175	6.82 ± 0.179	< 0.01	< 0.2	< 0.002
S. D.	1.87	1.68	1.04	..	..	..

* All the differences between the means are statistically significant, except for the difference between phosphorus levels of fasting babies and those fed human milk.

demonstrated that the calcium retention of premature infants on human milk is only about one-tenth of the daily retention in utero during the 10th lunar month (without vitamin D, one-twentieth to one-fiftieth). In Figure 9 the minimum calcium levels attained by each infant are plotted against the birth weight. It is obvious that up to a weight of 2500 gm. there is no correlation between birth weight and serum calcium level. However, there is an abrupt change at 2500 gm.; of 22 infants weighing more than 2500 gm. at birth only 3 had calcium levels below 8 mg. per 100 cc.; all three were sick infants.

The growth rate in this group of newborn infants could not be satisfactorily evaluated during the period of observation, since during the first two to three weeks of life body weight change may reflect shifts of body water and may not be related to actual growth of bones. Other criteria of the rate of growth were not available.

Rickets.—The possible role of rickets in the causation of hypocalcemia was consid-

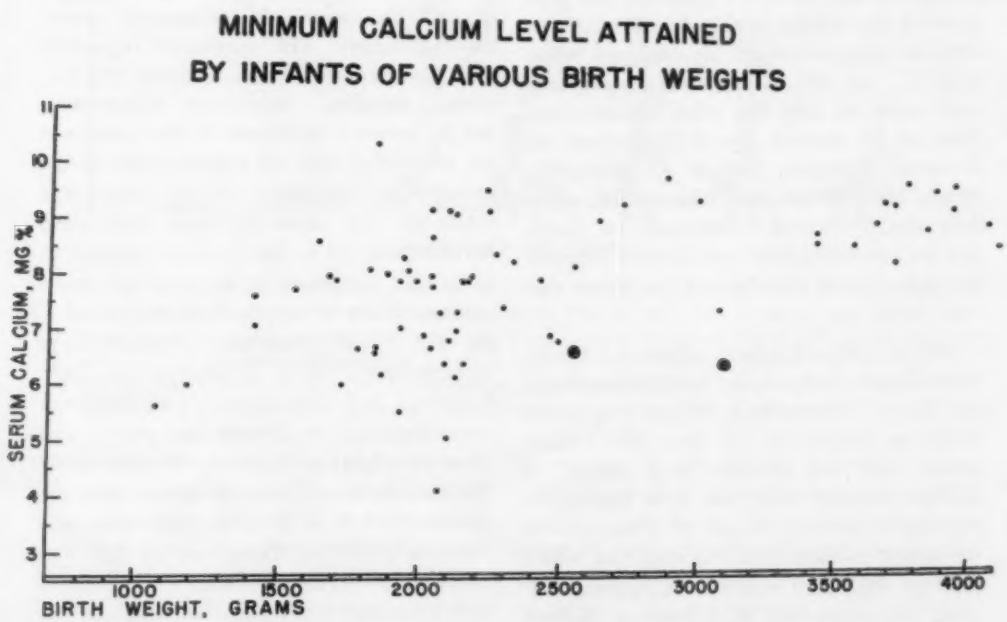


Fig. 9.—Minimum serum calcium level attained by each infant, plotted against birth weight. The two encircled dots represent infants of diabetic mothers, who had edema at birth.

ered. Phosphatase determinations were therefore done simultaneously with calcium and phosphorus determinations. As seen in Table 2, the mean phosphatase value was significantly higher for the premature than for the full-term infants, although both values are well within the range considered "normal" for this age.‖ In all full-term infants the phosphatase activity was below 8 B. U. per 100 cc. Only one premature infant (G. S.) had a phosphatase activity above 15 B. U. His course is described in the Appendix and Figure 5. The roentgenographic appearance of this infant's bones seems to correspond to the "ribbon-shaped, narrow zone of decreased density, lying some mm. proximally to the epiphyseal line" as described by von Sydow,[7] which was thought to be "prerachitic in most, though not all, cases." It is not claimed here that infant G. S. had rickets, but the data collected from this infant were more suggestive of rickets than those of any other patient. One other premature infant who was fed human milk reached a maximum phosphatase level of 12 B. U. on the 11th day of life. This infant's bone roentgenograms showed similar but less pronounced translucent zones. In all other infants the phosphatase activity remained below 12 B. U. per 100 cc. Bone roentgenograms were taken on only one other infant; these films, on the seventh day of life, showed no abnormal structure. Out of 33 patients in whom phosphatase was determined more than once, 14 showed a consistent rise. There was no consistent time relationship between the phosphatase activity and the serum calcium level.

Illness.—All six infants who were ill with other diseases had calcium levels below 8 mg. per 100 cc. (Appendix). No common factor could be implicated in these six infants except that two of them were infants of diabetic mothers and had been fasted for prolonged periods. In all of these infants the lowest calcium level was observed before feedings had been started. Subsequent calcium determinations in infants of diabetic mothers (not included in this study) also revealed hypocalcemia, and similar observations have been reported by other investigators.[2] None of the sick infants had a phosphatase level above 12 B. U. per 100 cc., and only one had a level above 8 B. U. The phosphorus levels tended to be high, but in two infants they were below 7 mg. per 100 cc.

Acidosis.—The pH and CO_2 content of the serum were determined 86 times in a total of 52 babies; on 64 occasions the pH was below 7.35. Five of the six sick infants and twenty-one additional infants had a pH below 7.30 at one time. The calcium levels in the samples with low pH were not significantly different from the average calcium levels in premature infants. Eleven infants had calcium levels taken both during and following a period of acidosis (pH less than 7.30). There was no consistent fall of serum calcium in the postacidotic period; in the majority of cases both the calcium and pH rose toward the end of the observation period (Fig. 5).

Symptoms of Tetany.—Very few of the premature infants with hypocalcemia had any of the commonly recognized symptoms of tetany. The symptoms registered were convulsions, hypersensitivity, rigidity, edema, vomiting, respiratory disturbance, and drowsiness. In Figure 10 the symptoms are correlated with the calcium level of the premature infant on the day the sample was obtained. The most striking observation from Figure 10 is the frequent absence of pathologic symptoms at all levels of serum calcium. Even at levels between 6 and 7 mg. per 100 cc., abnormal symptoms were noted in only 7 out of 22 observations. Only 8 patients had convulsions (1 of these not hypocalcemic), 14 patients had edema, and 15 were rigid or hypersensitive or both. The correlation of these symptoms with the calcium level at the time of observation was statistically not significant except for convulsions. In premature infants some of the symptoms under investigation here are not infrequently observed, even with normal serum calcium levels; in fact, drowsiness

‖ References 6 and 7

was observed more frequently with a serum calcium level above 8 or 10 mg. per 100 cc. than with lower levels.

On the other hand, convulsions, hypersensitivity, edema, shallow, irregular, labored respirations, and vomiting were only observed in 2 of the 21 full-term infants, and both of them had hypocalcemia at the time of the observations. None of the other full-term infants had hypocalcemia.

There was no clinically remarkable or statistically significant effect of the pH on the presence or absence of tetanic symptoms in patients with a serum calcium level of 8 mg. per 100 cc. or below. The symptoms considered for this purpose did not include drowsiness and respiratory irregularities, because the latter may be a cause and the former an effect of the low pH, irrespective of the calcium level.

Three premature infants died within the first three days of life; all three had symptoms and serum calcium levels compatible with tetany (Appendix).

Serum Potassium. — Serum potassium levels in the majority of all infants were in the "normal" range, between 4 and 6 mEq/liter. As seen in Table 2, the premature infants had a slightly but significantly higher mean potassium level than the full-term infants; both means are well within the normal range, but the standard deviation in the premature infants is rather large. Twelve samples in eight premature babies had potassium levels above 6 mEq/liter; in seven of these samples a simultaneously obtained serum calcium was 8 mg. per 100 cc. or below. The two patients with the highest potassium levels (9.1 and above 10 mEq/liter, respectively) were those who

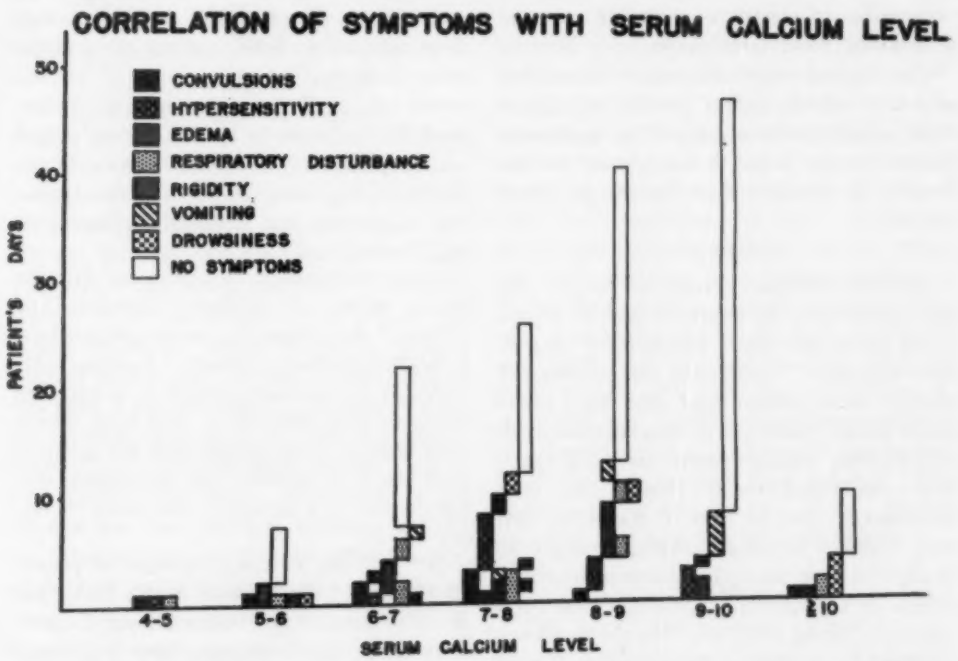


Fig. 10.—Pathologic symptoms observed in infants at various levels of serum calcium. The symbols for the various symptoms are indicated in the Figure. Each unit of the ordinate in each range of calcium levels indicates the symptoms present in one patient on the day on which this calcium level was determined, so that a patient who had four different symptoms on the same day will be represented by a horizontal bar of four units. The total height of each column indicates the total number of serum specimens with the particular calcium level.

subsequently died; they had convulsions and other symptoms of tetany at the time the high potassium and low calcium were observed. On four other occasions, when the potassium level was above 6 mEq/liter and the calcium level below 8 mg. per 100 cc., there were no symptoms. Five babies had a potassium level below 4 mEq/liter on one occasion each; one infant with a potassium level of 2.8 mEq/liter and a calcium level of 7.0 mg. per 100 cc. showed hypersensitivity and jitteriness. No definite conclusions as to the effect of the potassium level on the production of tetanic symptoms can be drawn from these observations.

The highest value for serum potassium seen in a full-term infant was 5.6 mEq/liter. Four infants on five occasions had potassium levels between 3 and 4 mEq/liter; no abnormal symptoms were noted in these infants.

COMMENT

Various etiologic factors for tetany and hypocalcemia of the newborn have been proposed in the literature: functional [10] or possibly anatomic [11] changes in the parathyroid glands, renal immaturity,¶ and high phosphate intake alone or in combination with parathyroid and/or renal factors # have been implicated; early rickets has been considered,* and in view of Ranström and von Sydow's histologic studies [24] might be thought of particularly in infants with serious illness or prematurity. Ranström's and von Sydow's [24] data suggested that the incidence of histologic rickets in infants dying during the first few days of life is much higher than had previously been expected, although Follis, Park and Jackson [25] found only two cases of infants under 2 weeks of age. A high incidence of hypocalcemia in premature infants † and in sick infants ‡ seems to be evident from the literature as well as in our experience. Since the intake of cow's milk with its high phosphorus content and low calcium: phosphorus ratio has been emphasized during the last several years,[12] it may be pertinent to point out that many of the cases of tetany of the newborn infant reported in the older literature occurred in breast-fed babies [10] or on the first or second day of life.[26] Graham, Barness, and György [9] found no correlation between the serum calcium level and the diet, although an effect of the diet on the phosphorus level was evident. Experiments on rats, which show conclusive evidence of the effect of the dietary calcium: phosphorus ratio on the serum calcium,[27] can apparently not be related to conditions in human infants except under special circumstances.[8] It is likely, therefore, that multiple or different factors are responsible for neonatal hypocalcemia in different cases.[2]

The present study, in agreement with the recent paper of Graham, Barness, and György,[9] shows that the serum calcium level in healthy, full-term infants is as remarkably stable in the newborn period as it has been found to be in later life.§ This level shortly after birth is never as high as in the umbilical cord blood, as Bakwin [3] has also pointed out, but it does not normally fall below 8 mg. per 100 cc.

By contrast, a large proportion of premature infants and all infants in this study who were otherwise sick were shown to have very labile and frequently very low serum calcium levels. Since low levels were often observed in premature infants who had no pathologic symptoms, one might be tempted to consider them "physiologic" for this group. Such a conclusion would be dangerous; the sudden transition from "latent tetany" into manifest tetany has been frequently observed, both in neonatal and in rachitic tetany, occasionally with disastrous results. The important effect of calcium ions on the excitability of nerves and muscles has long been known ‖; it is identical in animals

¶ References 1 and 23.

References 8, 11, and 12.

* References 6 and 7.

† References 10 and 26.

‡ References 1 and 2. Bruck, E., and Maitland, B.: Hypocalcemia, Exhibit at National Convention of the American Academy of Pediatrics, Atlantic City, N. J., November, 1948.

§ References 6, 28, and 29.

‖ References 29 and 30.

and man and does not permit us to consider serum levels of 6 or 7 mg. per 100 cc. as normal. Since premature infants are known to have lower serum protein levels than full-term infants,[31] it might be calculated that the ionized calcium in the serum of premature infants is not as low as it would be with the same total calcium level and a serum protein level of 7 gm. per 100 cc. The exact calculation of ionized calcium in the serum is probably impossible even when serum protein, phosphate, and citrate levels and pH are known; no formula has been developed which takes all these factors into consideration, although each of them is known to have an effect.¶ According to Ludewig's studies, 1 gm. of protein in the serum binds 0.15 mg. of calcium,[35] McLean and Hasting's nomogram [34] indicates an increase of Ca++ by 0.4-0.6 mg. per 100 cc. for a fall in plasma protein by 1 gm. per 100 cc., depending on the total calcium level (between 5 and 10 mg. per 100 cc.). According to these calculations one would not expect to find a "normal" figure for ionized calcium with a total serum calcium level of less than 7 mg. per 100 cc., no matter what the protein content is in the physiologic range. In the present study, neither protein nor citrate levels were determined, so no attempt has been made to calculate ionized or diffusible calcium. It is possible that the absence of pathologic symptoms in some patients with hypocalcemia was due to the fact that ionized calcium was not depressed as much as total calcium in the serum, but since this is not the case in all patients, a serum calcium level of 6 mg. per 100 cc. should still be regarded with alarm. In most infants, the serum calcium level rises to above 9 mg. per 100 cc. by the end of the first or second week of life without apparent change of the serum protein level. The stabilization at this level may be taken as an additional indication that the low levels observed during the early days of life are not "normal."

¶ References 32-34.

No single causative mechanism for the tendency to hypocalcemia stands out in these observations. The fasting period immediately after birth following the large calcium uptake in utero seemed to be most consistently correlated with a fall in serum calcium level. Lack of calcium supply may also be a factor in the hypocalcemia which frequently develops in young infants who are seriously ill with any disease. It may be assumed that the homeostatic mechanisms for maintaining the serum calcium level, like those controlling temperature, respiration, and other body functions,[36] are incompletely developed at birth in premature infants and are unable to cope with the radical alteration of calcium supply at birth or during illness which is associated with calcium starvation. Since calcium homeostasis is probably governed by parathyroid hormone, the parathyroid glands must be implicated in this mechanism. Pathologic-anatomic changes in the glands are not necessary to explain insufficiency in the face of such extreme demands. Excess circulating phosphate from hemolysis and other cell breakdown after birth or later from cow's milk may contribute to these demands, but the inconsistent relationship between serum calcium and phosphorus levels in the present data indicates that phosphorus is only one of several factors in a complex interplay of mechanisms.

SUMMARY

The blood serum levels of calcium, inorganic phosphorus, phosphatase, potassium, CO_2, and pH were determined repeatedly in 51 premature and 21 full-term newborn infants during the first two weeks of life as an endeavor to elucidate the incidence and the causation of hypocalcemia in the newborn period.

The serum calcium level of the premature infants in general was considerably lower and fluctuated more widely than that of the full-term infants.

The lowest calcium level in an individual infant usually was observed during the immediate postnatal fasting period. The longer the fasting period was extended, the lower,

in general, were the serum calcium levels observed.

In the level of inorganic phosphorus, there was no significant difference between premature and full-term infants.

When fasting was prolonged for more than 36 hours, or when cow's milk was fed, the phosphorus level rose. When human milk was fed, it usually fell.

When it was attempted to correlate the rise or fall of calcium and inorganic phosphorus levels from one blood sample to the next in the same infant, it was seen that in 69% of the intervals between blood samples the calcium level rose whether the phosphorus rose or fell. In 31% of the intervals, the calcium level fell; this fall was usually associated with a rising phosphorus level.

In individual infants, the curves of calcium and phosphorus levels run as often parallel as in opposite directions.

Blood levels during the initial fast were compared with those after the infant had been fed. When human milk was fed, the calcium level rose consistently, the phosphorus level rose in about one-third of the cases and fell in two-thirds. When cow's milk was fed, calcium rose in 60% of the cases and fell in 40%; phosphorus rose in 73% of cases and fell in 27%; the mean calcium and the mean phosphorus on cow's milk were higher than before feeding.

The phosphatase levels were not indicative of rickets.

The minimum calcium level attained was not related to the birth weight within the range between 1400 and 2500 gm. The rate of growth during the sampling period (one to three weeks) could not be evaluated from the weight gain and therefore could not be correlated with serum calcium levels.

The calcium and phosphorus levels of the cord blood showed no relation to the subsequent values.

Few of the premature infants with hypocalcemia had any of the commonly recognized symptoms of tetany. The correlation of these symptoms with the calcium level at the time of observation was statistically not significant, except for convulsions.

All six infants ill with other diseases had serum calcium levels below 8 mg. per 100 cc. Three infants died; all had symptoms and blood calcium levels of tetany.

The pH and potassium levels had no clinically remarkable or statistically significant effect on the presence or absence of tetanic symptoms in patients with hypocalcemia.

The causes of hypocalcemia in newborn infants are probably multiple and interrelated in a complicated manner.

APPENDIX

Report of Cases

Two infants were born of diabetic mothers. D. W. was born after 7½ months' gestation, weighing 2551 gm., with edema. At 46 hours of age, before any feedings, she weighed 2325 gm. and was edematous and jittery. Calcium 6.6 mg. per 100 cc., phosphorus 9.1 mg. The next day, twitching of the legs was noted. Feedings (Alacta [powdered half-skimmed cow's-milk preparation]) were begun. On the fifth day the serum calcium was 8.5 mg. per 100 cc., phosphorus 7.95 mg. The further course was uneventful.

S. G. was born at term, weighing 3090 gm., with edema. After 45 hours, before any feeding, edema was still present; the baby was drowsy, jittery, and vomiting and had shallow, irregular respirations with marked distress. Serum calcium was 6.3 mg. per 100 cc., phosphorus 14.5 mg., pH 7.15, CO_2 25.9 mEq/liter.

Boy S. weighed 1417 gm. at birth. From the first day of life on, he had convulsions, hypersensitivity, irregular, labored respirations, and edema. He was never fed and lost 16% of his birth weight. At 3 days of age he died during an exploratory laparotomy without general anesthesia. He had complete atresia of the duodenum. Blood studies done on the second and fourth days revealed a serum calcium between 7.1 and 7.3 mg. per 100 cc., phosphorus of 9.6 to 9.4 mg., pH 7.25, CO_2 content 19 mEq/liter, and potassium 9.1 to 6.7 mEq. Necropsy revealed no pneumonia or atelectasis.

Baby Fe. was born of a toxemic mother and was asphyctic at birth. After respirations were established, they remained rapid, grunting, and irregular. The infant had convulsions, a strongly positive Chvostek sign, shrill cry, rigidity, and edema of the thorax. A serum calcium level was 5.5 mg. per 100 cc., the phosphorus level 10.8 mg. The infant died 34 hours after birth in the tonic phase of a convulsion. There was no postmortem examination.

Girl Pl. had irregular shallow labored respirations, convulsions, and rigidity. Serum calcium 20 hours after birth was 6.9 mg. per 100 cc., phosphorus 5.1 mg., pH 7.12 with a CO_2 content of 24.5 mEq/liter, and potassium of 4.8 mEq. The next day symptoms persisted, with a calcium level of 7.6 mg. per 100 cc., and the infant died. She had never been fed. Necropsy revealed tetralogy of Fallot, with a widely patent ductus arteriosus (which should not have caused these symptoms and death at the age of 2 days) and hemorrhagic suffusions in the lungs.

N. M. weighed 3090 gm. at birth. From the first day on, he had twitching and convulsions, which recurred frequently during the first week. He was drowsy and during the first three to four days had a strongly positive Chvostek sign and shallow, irregular, labored respirations. He was therefore not fed for the first two days and was kept in oxygen. At 18 hours of age, blood glucose was 28 mg. per 100 cc., later 19 mg. Serum calcium was 7.5 mg. per 100 cc., phosphorus 6.9 mg, pH 7.21, CO_2 content 24.9 mEq/liter. Intravenous calcium gluconate and oral glucose water were then administered. On the third to fifth days of life, blood glucose remained at 20-30 mg. per 100 cc., from the sixth day on it was above 60 mg. Serum calcium rose after therapy to 8.2-8.8 mg. per 100 cc., but on the sixth day of life was 7.4 mg. again and convulsive activity and vomiting continued. Evaporated-milk feeding and vitamin D were begun on the fifth day. The infant recovered; on the 13th day the calcium level was 9.9 mg. per 100 cc. This child had two subsequent hospital admissions, at the ages of 20 and 25 months, for spontaneous hypoglycemia with convulsions. He was last seen at the age of 5 years, in good health.

G. S. weighed 2098 gm. at birth and had some edema of his hands and feet for the first day or two. He developed jaundice (maximum serum bilirubin level 11.9 mg. per 100 cc. on the sixth day of life); stool and urine had normal color. He was fed an Alacta (proprietary powdered half-skimmed cow's-milk preparation) formula. The levels of calcium and phosphorus in his serum are portrayed in Figure 5.# The phosphatase activity in his cord blood was 13.4 Bodansky units; it remained between 12 and 15.8 units for 11 days. During this same period he had profound hypocalcemia, although calcium in the cord blood serum had been 11.5 mg. per 100 cc. The serum calcium started to rise and the phosphatase to fall during the second week of life, after administration of vitamin D had been begun. Roentgenograms of this infant's bones showed a striking translucent zone near the ends of the metaphyses of all long bones.

His initials in Figure 5 are erroneously marked S. H.

REFERENCES

1. Snelling, C. E.: Disturbed Kidney Function in the Newborn Infant Associated with Decreased Calcium: Phosphorus Ratio, J. Pediat. **22**:559 (May) 1943.

2. Dodd, K., and Rapoport, S.: Hypocalcemia in the Neonatal Period: A Clinical Study, Am. J. Dis. Child. **78**:537 (Oct.) 1949.

3. Bakwin, H.: Tetany in Newborn Infants, J. Pediat. **14**:1 (Jan.) 1939.

4. Denzer, B. S.; Reiner, M., and Weiner, S. B.: Serum Calcium in the Newborn, Am. J. Dis. Child. **57**:809 (April) 1939.

5. Todd, W. R.; Chuinard, E. G., and Wood, M. T.: Blood Calcium and Phosphorus in the Newborn, Am. J. Dis. Child. **57**:1278 (June) 1939.

6. Barnes, D. J., and Munks, B.: Serum Phosphatase, Calcium, and Phosphorus Values in Infancy, Proc. Soc. Exper. Biol. & Med. **44**:327 (June) 1940.

7. von Sydow, G.: A Study of the Development of Rickets in Premature Infants, Acta Pædiat. (Supp. 2) **33**:3, 1946.

8. Gittleman, I. F., and Pinkus, J. B.: Influence of Diet on the Occurrence of Hyperphosphatemia and Hypocalcemia in the Newborn Infant, Pediatrics **8**:778 (Dec.) 1951.

9. Graham, G. G.; Barness, L. A., and György, P.: Serum Calcium and Inorganic Phosphate in the Newborn Infant, and Their Relation to Different Feedings, J. Pediat. **42**:401 (April) 1953.

10. Bakwin, H.: Pathogenesis of Tetany of the Newborn, Am. J. Dis. Child. **54**:1211 (Dec.) 1937.

11. Gardner, L. I.: Tetany and Parathyroid Hyperplasia in the Newborn Infant: Influence of Dietary Phosphate Load, Pediatrics **9**:534 (May) 1952.

12. Gardner, L. I.; MacLachlan, E. A.; Pick, W.; Terry, M. L., and Butler, A. M.: Etiologic Factors in Tetany of Newly Born Infants, Pediatrics **5**:228 (Feb.) 1950.

13. Rapoport, S.; Dodd, K.; Clark, M., and Syllm, I.: Postacidotic State of Infantile Diarrhea: Symptoms and Chemical Data; Postacidotic Hypocalcemia and Associated Decreases in Levels of Potassium, Phosphorus and Phosphatase in Plasma, Am. J. Dis. Child. **73**:391 (April) 1947.

14. American Academy of Pediatrics, Committee on Fetus and Newborn: Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature, Evanston, Ill., The American Academy of Pediatrics, 1948.

15. Sobel, A. E., and Sobel, B. A.: Microestimation of Calcium in Serum, J. Biol. Chem. **129**: 721 (Aug.) 1939.

16. Gomori, G.: A Modification of the Colorimetric Phosphorus Determination for Use with the Photoelectric Colorimeter, J. Lab. & Clin. Med. **27**:955 (April) 1942.

17. Bodansky, A.: Phosphatase Studies: II. Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93 (June) 1933.

18. Stearns, G.: The Mineral Metabolism of Normal Infants, Physiol. Rev. **19**:415 (July) 1939.

19. Hamilton, B., and Moriarty, M.: The Composition of Growth in Infancy: A Premature Infant, Am. J. Dis. Child. **37**:1169 (June) 1929.

20. Givens, M. H., and Macy, I. G.: The Chemical Composition of the Human Fetus, J. Biol. Chem. **102**:7 (Sept.) 1933.

21. Hamilton, B.: The Calcium Metabolism of Premature Infants, Am. J. Dis. Child. **20**:316 (Oct.) 1920.

22. Benjamin, H. R.; Gordon, H. H., and Marples, E.: Calcium and Phosphorus Requirements of Premature Infants, Am. J. Dis. Child. **65**:412 (March) 1943.

23. McCrory, W. W.; Forman, C. W.; McNamara, H., and Barnett, H. L.: Renal Excretion of Phosphate in Newborn Infants: Observations in Normal Infants and in Infants with Hypocalcemic Tetany, Am. J. Dis. Child. **80**:512 (Sept.) 1950.

24. Ranström, S., and von Sydow, G.: Rickets in Newborn Infants: Clinical and Histologic Study, Pediatrics **4**:406 (Oct.) 1949.

25. Follis, R. H., Jr.; Park, E. A., and Jackson, D.: The Prevalence of Rickets at Autopsy During the First 2 Years of Age, Bull. Johns Hopkins Hosp. **91**:480 (Dec.) 1952.

26. Willi, H.: Die Neugeborenenspasmophilie, Monatsschr. Kinderh. **80**:309 (Nov.) 1939.

27. Stoerk, H. C., and Carnes, W. H.: The Relation of the Dietary Ca:P Ratio to Serum Ca and to Parathyroid Volume, J. Nutrition **29**:43 (Jan.) 1945.

28. Howland, J., and Kramer, B.: Calcium and Phosphorus in the Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

29. Kramer, B.; Tisdall, F. F., and Howland, J.: The Clinical Significance of Calcium Concentration in the Serum of Children and Possible Errors in Its Determination, Am. J. Dis. Child. **22**:560 (Dec.) 1921.

30. Howland, J., and Kramer, B.: A Study of the Calcium and Inorganic Phosphorus in the Serum in Relation to Rickets and Tetany, Monatsschr. Kinderh. **25**:279 (March) 1923.

31. Rapoport, M.; Rubin, M. I., and Chaffee, D: Fractionation of the Serum and Plasma Proteins by Salt Precipitation in Infants and Children: 1. The Changes with Maturity and Age; 2. The Changes in Glomerulonephritis; 3. The Changes in Nephrosis, J. Clin. Invest. **22**:487 (July) 1943.

32. Howard, J. E.: Normal Calcium and Phosphorus Transport and Body Fluid Homeostasis, in: Metabolic Interrelations with Special Reference to Calcium: Transactions of the Fifth Conference, January 5-6, 1953, New York, Josiah Macy, Jr., Foundation, 1954, pp. 12-16.

33. Ludewig, S.; Chanutin, A., and Masket, A. V.: Studies on the Calcium-Protein Relationship with the Aid of the Ultracentrifuge: II. Observations on Serum, J. Biol. Chem. **143**:753 (May) 1942.

34. McLean, F. C., and Hastings, A. B.: The State of Calcium in the Body Fluids, J. Biol. Chem. **108**:285 (Jan.) 1935.

35. Smith, C. A.: The Physiology of the Newborn Infant, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1951.

Studies of Tocopherol Deficiency in Infants and Children

I. Hemolysis of Erythrocytes in Hydrogen Peroxide

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In 1949, Owens and Owens [1] suggested that defective absorption of fat by premature infants * and the use of partially skimmed-cows'-milk mixtures † might lead to a deficiency of vitamin E. Support for the latter concept was obtained by Wright, Filer, and Mason,[9] who reported that the serum tocopherol levels of premature infants fed partially skimmed cows' milk decreased from average levels of 0.4 mg. per 100 cc. at birth to 0.1 mg. at age 31-40 days. Other investigators reported average levels of 0.25 to 0.5 mg. per 100 cc. for premature infants fed unsupplemented diets,‡ well below the level of approximately 1 mg. per 100 cc. found in full-term infants fed at the breast.[9]

György and Rose § reported that the erythrocytes of vitamin-E-deficient rats were hemolyzed by suitable incubation with dialuric acid and that this hemolysis was preventable either by feeding tocopherol or by its addition to the in vitro incubation mixture. They subsequently showed that a dilute solution of hydrogen peroxide could be used instead of dialuric acid and that the erythrocytes of newborn full-term infants showed some susceptibility to hydrogen peroxide.‖ Although the red blood cells of premature infants few cows'-milk mixtures were not hemolyzed in dialuric acid,[16] they were hemolyzed in hydrogen peroxide, and this susceptibility could be regularly reversed by the administration of tocopherol [17] in one infant in a dose as low as 1.0 mg. of *dl-a*-tocopherol acetate daily.[18] The effectiveness of doses as low as 2.5 mg. daily has been reported by Mackenzie,[19] who also showed that a significant degree of hemolysis was absent when the serum tocopherol concentration was raised above 0.5 mg. per 100 cc. but was irregularly present when the tocopherol concentration was below this level.

It is the purpose of this report to present data on hemolysis of erythrocytes of unfed premature and full-term infants, of young infants thriving on customary diets, of a group of malnourished infants and children with and without steatorrhea, and of infants and children admitted to the hospital with a variety of less common diseases. Some data previously presented ¶ are included in this report. Data on plasma tocopherol levels and on the mechanism of hemolysis will be presented in future reports.

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* References 2-6.

† References 7 and 8.

‡ References 1, 10, and 11.

§ References 12 and 13.

‖ References 14 and 15.

¶ References 17, 18, and 20.

METHODS

The hemolysis test is performed with only minor modifications of the procedure of György, Cogan, and Rose.# Approximately 0.2 ml. of blood is drawn from an antecubital vein into a syringe previously rinsed with sterile 1% sodium citrate in 0.9% saline solution. In newborn infants with a high hematocrit, less blood may be used, since only 0.1 ml. of packed red blood cells permits testing in triplicate. Attempts to use blood which dripped from the umbilical cord at birth were discarded because in three of eight simultaneous determinations on such blood and blood drawn from an umbilical vein hemolysis of venous blood was significantly higher.* Simultaneous studies of venous and capillary blood, the latter obtained by heel stick, showed good correlation. All tests were begun within one hour after blood was drawn. Attempts to increase this time interval or to decrease the duration of incubation led to variable results and were therefore discarded as possible modifications of the test.

The blood is transferred to a graduated centrifuge tube containing 2.0 ml. of the citrate-saline solution. After centrifugation for 10 minutes at 1800 rpm, the volume of cells is estimated and the supernatant fluid withdrawn. The cells are then made up to a 2.5% suspension in a saline-buffer mixture of equal parts of 0.9% saline and phosphate buffer (0.2 M potassium monophosphate, 25.0 ml.; 0.2 M sodium hydroxide, 19.7 ml.; H_2O to 100.0 ml., pH 7.4) and incubated at 37 C for 15 minutes. After centrifugation and withdrawal of the supernatant, they are resuspended, 5% in 0.9% saline. Into each of five small round-bottom test tubes, 0.25 ml. of suspension is pipetted, after shaking to assure a uniform suspension. Into four of these tubes 0.25 ml. of 2.4% hydrogen peroxide in phosphate buffer is measured (1 cc.—30% H_2O_2—superoxal r + 11.5 cc., phosphate buffer). Into the fifth tube 0.25 ml. of phosphate buffer is pipetted as a control. All tubes are incubated at 37 C for 15 minutes, then gently shaken on a laboratory shaker at room temperature for two and three-quarters hours. At the end of this three-hour period, 4.5 ml. of saline-buffer is added to the control and to three of the tubes to which H_2O_2 had been added. To the fourth tube containing peroxide, 4.5 ml. of distilled water is added. The tubes are mixed by inversion and centrifuged, and the color of the supernatant fluid read in a photoelectric colorimeter using a 540 mμ filter. The per cent of hemolysis caused by peroxide in each tube is calculated from the ratio of the mean reading for the supernatants of tubes containing peroxide and saline buffer to the reading of the supernatant of the tube containing peroxide and distilled water, both values having been corrected by subtracting the reading of the control supernate. Ordinarily very little hemolysis was present in the control; occasionally, in tests run regularly on the blood of E-deficient rats as a biologic control of the test, the control would show a high reading as though the prolonged use of the E-deficient diet produced some increased fragility of the cells. A high control occasionally occurred with an infant's blood, suggesting either contamination of a tube with water or rough handling of the cells; this was very rare, and results of such tests were discarded. Tests in which duplicate readings did not check within ± 5% were discarded; actually this accuracy was usually obtained in triplicate.

Tests showing more than 50% hemolysis were arbitrarily designated as markedly positive. Blood from adults almost uniformly showed less than 10% hemolysis. Plasma tocopherol determinations were made in a large number of subjects at the same time as the hemolysis tests; these results will be presented in another report.

SUBJECTS

The infants and children consisted of the following groups:

(1) Newborn infants, either unfed or fed small amounts of glucose water.

A. Full term—282.

B. Premature—67.

The full-term newborn infants were born on either the private or ward service of the Sinai Hospital, and blood was drawn during the first 24 hours of life, before any milk feedings had been given. They ranged in weight from 2550 to 4480 gm. The premature infants were either born at the Sinai Hospital or admitted to the premature nursery of the Harriet Lane Home from the Women's Clinic of The Johns Hopkins Hospital or from other hospitals or home deliveries. They ranged in weight from 600 to 2410 gm.

(2) Young well babies.

A. Infants born at term and examined in the well-baby clinic of the Sinai Hospital at the time of a routine postpartum visit of the mother to the obstetric clinic—72. The average age was 48 days, range 9 to 81 days. Fifty-four infants had been fed ordinary cows'-milk mixtures, and eighteen had been entirely or predominantly breast-fed. Several had received small, usually unprescribed amounts of cereal for from one to three weeks; no effect of this on the hemolysis test was noted.

B. Infants born prematurely and studied while still in the nurseries—137. All infants had been fed partially skimmed-cows'-milk mixtures, although some received evaporated-milk mixtures for a few days before the observations. They ranged in age

References 14 and 15.

* Some of these determinations were made at the Walter Reed Army Hospital by Capt. Frank J. Cozetto (MC).

from 4 to 94 days at the time of the final tests, which are the only ones recorded in this section.

In 14 infants serial observations are available for periods of at least 14 days.

(3) Seventeen sick full-term infants admitted to the hospital because of a variety of acute febrile or nonfebrile illnesses. They ranged in age from 5 to 158 days. They had been fed unskimmed-cows'-milk mixtures, some with variable amounts of semi-solid foods, prior to admission and were studied after 2 to 14 days on diets of cows'-milk mixtures from which all or half of the cream had been removed.

(4) Infants and children with malnutrition.

A. Twenty-three observations were made in 13 infants and children with cystic fibrosis of the pancreas, 5 in one child with familial steatorrhea, 3 in 2 infants with celiac syndrome, and 7 observations in 4 infants or children with obstructive jaundice. These subjects ranged in age from 3 months to 14 years. Most of the subjects were receiving diets in which the fat intake had not been reduced; for some a low-fat intake had been both prescribed and followed.

B. Twenty-one observations were made in infants and children of the same age group as the patients with steatorrhea. Some of these had malnutrition associated with infection such as bronchiectasis, tuberculosis, or rheumatic fever; others had malnutrition associated with hydrocephalus, pyloric stenosis, cerebral palsy, congenital heart disease.

(5) Infants and children with a variety of less common diseases on ordinary diets.

A. Blood dyscrasias—11.

B. Other diseases—16.

In 23 premature and 8 full-term infants and in 12 infants and children with malnutrition and steatorrhea, emulsions of *dl*-α-tocopherol acetate were given and the effect on the hemolysis test noted. None of the infants and children received iron medication during the period of study. Most of them received ascorbic acid and water-soluble supplements of vitamins A and D.

RESULTS

(1) *Unfed Newborn Infants.*—The results of 282 observations in full-term infants and 67 observations in premature infants are presented in Table 1 as the mean per cent hemolysis and as the proportion of observations showing hemolysis below 10% or above 50%. It is seen that a large proportion of each group of infants, (25% to 56%) showed more than 50% hemolysis and that the mean hemolysis ranged from 34% to 53%. This represents a considerable degree of susceptibility when compared with normal adults or premature or full-term infants fed emulsions of *dl*-α-tocopherol acetate; for such subjects hemolysis is almost uniformly less than 10%.

TABLE 1.—*Hemolysis in H_2O_2 of Erythrocytes of Unfed Newborn Infants*

	Observations, No.	Hemolysis (Mean±S.E.), %*	Observations with Hemolysis, per Cent: Less Than 10%	Observations with Hemolysis, per Cent: More Than 50%
Full Term				
Private White	81	34±3.23	26	25
Service White	133	43±2.43	14	45
Service Negro	68	49±4.06	16	48
Premature				
White†	42	35±4.33	21	31
Negro	25	53±6.12	8	56

* Ratio of hemoglobin liberated from aliquots of red blood cells incubated in hydrogen peroxide and diluted with a buffer to that liberated by dilution in distilled water.

† Inadequate information made it impractical to attempt to divide this small group of premature infants according to economic status.

No statistically significant differences were found when one compared mean hemolysis values of full-term and premature infants, either in the white or Negro groups. Significant differences were found, however, when one compared the means for premature white and premature Negro infants (difference ± S.E. difference = 18% ± 7.61, $p < 0.02$), the full-term private white and service white infants (9% ± 4.04, $0.01 < p < 0.05$), the full-term private white and full-term Negro patients (15% ± 5.16, $p < 0.01$). The difference between the means for full-term service white and full-term Negro patients was not statistically significant (6% ± 4.71,

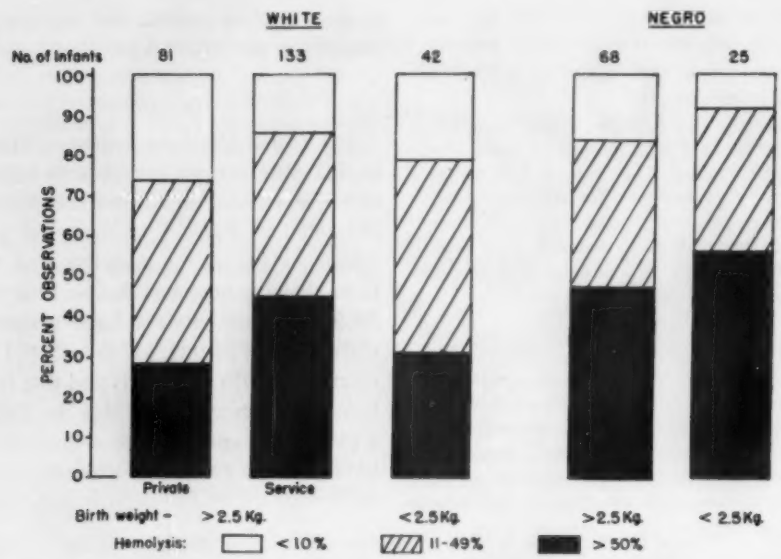

Fig. 1.—Hemolysis in hydrogen peroxide of erythrocytes of unfed newborn infants—relation of proportion of markedly positive tests (more than 50% hemolysis) and negative tests (less than 10% hemolysis) to maturity and economic status of mothers.

TABLE 2.—*Hemolysis in H_2O_2 of Erythrocytes of Full-Term Well Babies*

No.	Diet	Av. Age, Days	Hemolysis (Mean±S.E.), %	Observations with Hemolysis, per Cent: Less Than 10%	Observations with Hemolysis, per Cent: More Than 50%
White					
133	Unfed	Newborn	43±2.43	14	45
29	Cows' milk*	46	21±4.10	55	14
7	Breast milk	46	4	100	0
Negro					
68	Unfed	Newborn	49±4.08	16	48
25	Cows' milk*	46	31±4.80	32	24
11	Breast milk	44	11	73	9

* The cows'-milk mixture consisted of ordinary dilutions of evaporated milk with added carbohydrate. Some infants had received small amounts of cereal for 1-3 wk. prior to the test.

$p > 0.1$). The data are presented graphically in Fig. 1.

(2) *Young Well Babies.*—A. Full-Term Babies: Observations were made on 29 service white and 25 Negro well babies at an average age of 7 weeks. They had been fed ordinary dilutions of evaporated milk with added carbohydrate, and a few had received small amounts of cereal. For the white infants the mean hemolysis had dropped from 43% in the newborn period to 21% (22%±4.76, $p<0.001$), and for the Negro infants from 49% to 31% (18%±6.23, $p<0.01$). In 10 infants, observations were made both in the newborn period and later in the well-baby clinic at ages varying from 9 to 64 days. These results are presented in Table 3. The mean hemolysis decreased from 52% to 26%, five infants showing decreases of from 23% to 81%, four virtually no change, and one an increase of 17%.

Eighteen infants who were entirely or almost entirely breast-fed were tested at ages 35 to 60 days (Table 2). The mean hemolysis was only 8%. All 7 white infants and 8 of 11 Negro infants shows less than 10% hemolysis. The remaining three Negro infants showed 13%, 30%, and 59% hemolysis.

TABLE 3.—*Hemolysis in H_2O_2 of Erythrocytes of Ten Full-Term Infants Studied at Birth and in Well-Baby Clinic*

Infant	Race	Age at Retest, Days	Hemolysis, per Cent	
			Birth	Retest
R	N	49	2	1
W	N	58	15	32
H	W	43	20	19
D	W	50	25	2
J	W	59	58	64
M	N	53	60	2
C	W	64	66	3
S	N	9	80	30
C	N	38	80	86
P	N	30	100	19
		Mean	52	26

did not rise, but neither did it decrease as in the full-term Negro infants.

In 14 infants serial determinations were made for at least 14 days while they were fed cows'-milk mixtures, for the most part partially skimmed. Seven examples are presented in Fig. 2 to indicate the range of variability. For infant T., hemolysis remained below 10% over a 20-day period. In contrast, Infant Q showed marked hemolysis (85% to 100%) over the whole period of observation from age 14 to 55 days. Infant McC. also showed hemolysis above 50% over a period from age 2 to 58 days. For

TABLE 4.—*Hemolysis in H_2O_2 of Erythrocytes of Premature Infants Fed Cows'-Milk Mixtures**

Age	Observations, No.	Hemolysis (Mean±S.E.), %	Observations with Hemolysis, per Cent	
			Less Than 10%	More Than 50%
White				
Unfed newborn	42	35±4.33	21	31
Less than 30 days	43	59±4.88	9	58
30 days and more	41	69±4.53	5	76
Negro				
Unfed newborn	25	52±6.12	8	56
Less than 30 days	31	62±5.21	0	61
30 days and more	22	53±7.35	14	55

* Only the last test performed for each infant is included in this table. Although some of the older infants were receiving unskimmed-cows'-milk mixtures at the time of testing, partially skimmed milk had been fed during most of the period before the test

B. *Premature Well Babies*: In Table 4 are presented the results of 137 observations on premature infants who had been fed partially skimmed cows'-milk mixtures either throughout or for the major part of their stay in the nurseries. Although multiple observations were available on some infants, only the final observations are presented in order to permit comparison with the full-term babies seen in the well-baby clinic. In contrast with the findings in the latter infants, whose hemolysis had shown a definite decrease (Table 2), the white premature infants showed an increase in mean hemolysis from 35% for the newborn group to 59% for the infants less than 30 days and 69% for the infants more than 30 days of age. Differences between the unfed newborn infants and each of the two groups of older infants were statistically significant ($24\% \pm 6.52$, $p < 0.001$; $34\% \pm 6.12$, $p < 0.001$). For the Negro infants, the mean hemolysis wholly undetermined reasons, perhaps technical, the hemolysis tests varied from 91% to 52% to 96% over a six-day period from age 26 to 32 days although there had been no change in his diet. Infant B is the only infant who showed a decrease in hemolysis with increasing age and duration of the diet; his last test, at age 13 days, showed a suggestive rise. No explanation is available for the decrease shown, which may also have occurred in infant Mo.; these infants were not receiving colostrum, which is high in tocopherol.†

(3) *Young Full-Term Infants with Acute Illnesses.* — Thirty-four observations were made on seventeen infants ranging in weight from 2600 to 7000 gm. and in age from 5 to 158 days who were admitted to the hospital because of various febrile or nonfebrile illnesses. The infants had all received un-

† References 21-23.

skimmed cows'-milk mixtures before admission to the hospital and either completely or partially skimmed cows'-milk mixtures after admission. Initial observations made from 2 to 14 days after beginning the low-fat diet showed hemolysis over 50% in 12 of the 17 infants. One infant showed a rise in hemolysis from 1% on the third day of the diet to 59% on the seventh day. In contrast, another infant showed virtually the same degree of hemolysis on the 11th day as on the 3d day of the diet, 2% and 12%, respectively.

The feeding of *dl*-α-tocopherol acetate ‡ to 8 full-term and to 23 premature infants led to prompt reversal of the hemolysis test, as has been previously reported.§ In Fig. 3 are presented the results with two full-term and two premature infants given supplements of α-tocopherol acetate of 1.5 to 6.0 mg. daily (0.6 to 2.0 mg/kg.). In all four infants reversal took place; determination of the size of a uniformly effective dose requires study of many more infants.

(4) *Infants and Children with Chronic Malnutrition.* — Thirty-eight observations were made in malnourished subjects with steatorrhea, and twenty-one subjects of comparable age, i. e., up to fifteen years, with malnutrition due to other causes. Of the children with steatorrhea, 13 had cystic fibrosis, 2 celiac syndrome, 4 obstructive jaundice, and 1 familial steatorrhea. Thirty, or 79% of the observations showed over 50% hemolysis, and four of the eight tests below 50% were in subjects who were receiving pancreatin. Of the 21 observations in subjects without steatorrhea, only 2 showed hemolysis over 50%; these were in an infant with eczema

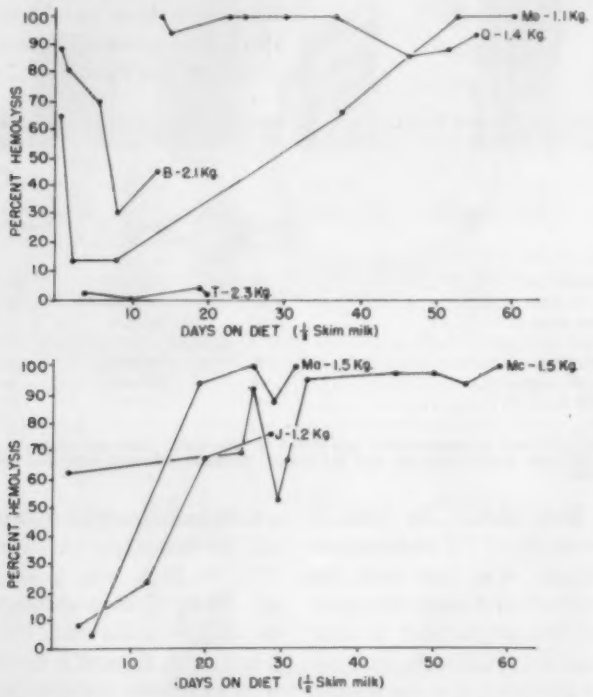

Fig. 2.—Hemolysis in hydrogen peroxide of erythrocytes of seven premature infants. Serial determinations indicate trend with increasing age and duration of low tocopherol intake. Birth weight is indicated for each infant.

‡ The emulsion of *dl*-α-tocopherol acetate used in most observations was supplied by Dr. Leo Pirk, Hoffmann-La Roche Co., Nutley, N. J.

§ References 17, 19, and 20.

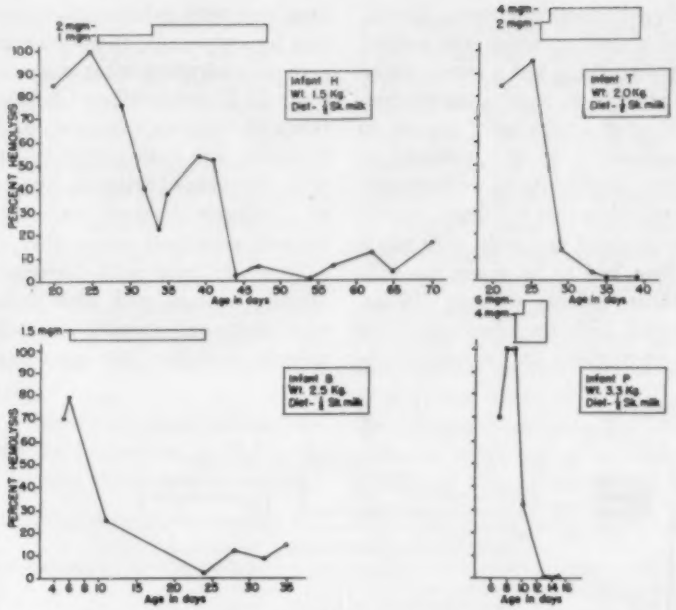

Fig. 3.—Effect of small doses of tocopherol acetate on hemolysis in hydrogen peroxide of erythrocytes of two premature and two full-term infants fed low-tocopherol diets. The tocopherol supplements ranged from 1 to 6 mg. daily of an emulsion of the acetate. The average weight during the observation is indicated for each infant.

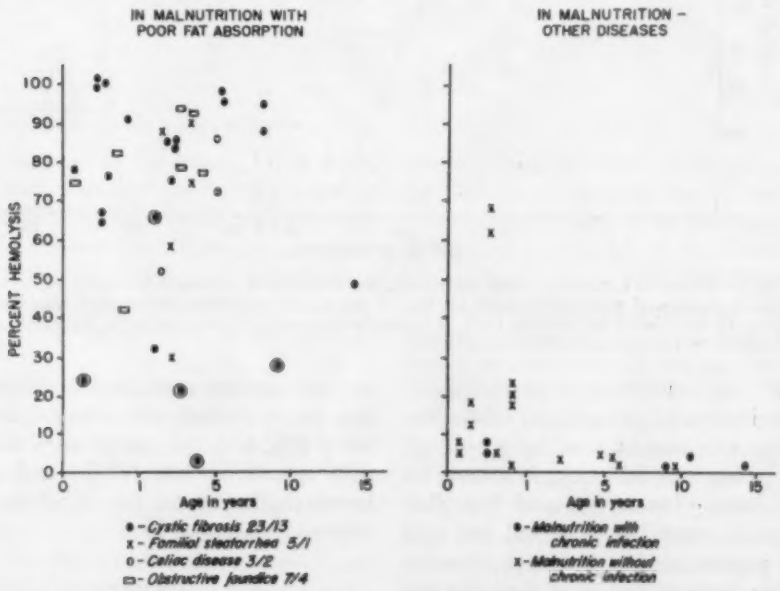
IN MALNUTRITION WITH POOR FAT ABSORPTION
IN MALNUTRITION - OTHER DISEASES
PERCENT HEMOLYSIS
Age in years
● - Cystic fibrosis 23/13
x - Familial steatorrhea 5/1
o - Celiac disease 3/2
□ - Obstructive jaundice 7/4
● - Malnutrition with chronic infection
x - Malnutrition without chronic infection

Fig. 4.—Hemolysis in hydrogen peroxide of erythrocytes of infants and children with malnutrition either with or without diseases associated with steatorrhea. The number of observations and number of patients with different causes for steatorrhea are indicated by number after each disease. The circled dots in the left half of the figure represent subjects with cystic fibrosis who were receiving pancreatin at the time of observation. Markedly positive hemolysis tests (more than 50%) were obtained in older children as well as in young infants.

who had developed hypoproteinemia, edema, and anemia on a diet in which his mother had eliminated everything but a cereal-water mixture in an attempt to control his eczema. Administration of *dl*-α-tocopherol acetate to this infant produced a prompt reversal of the hemolysis test. In the infants with steatorrhea, particularly when due to biliary atresia, reversal when obtained was only with much larger doses than had to be given the full-term or premature infants without disease. This is in accord with the observations of Filer and his co-workers on tocopherol absorption.[24] An example is given in Fig. 5. The effectiveness of preparations other than the acetate emulsion is now being studied, as is the relation of hemolysis to plasma tocopherol levels. The addition of free *dl*-α-tocopherol in vitro has protected red cells of these patients against hydrogen peroxide even when supplementation of their diet has produced no reversal of the test; the amount needed for in vitro reversal was not unusual.

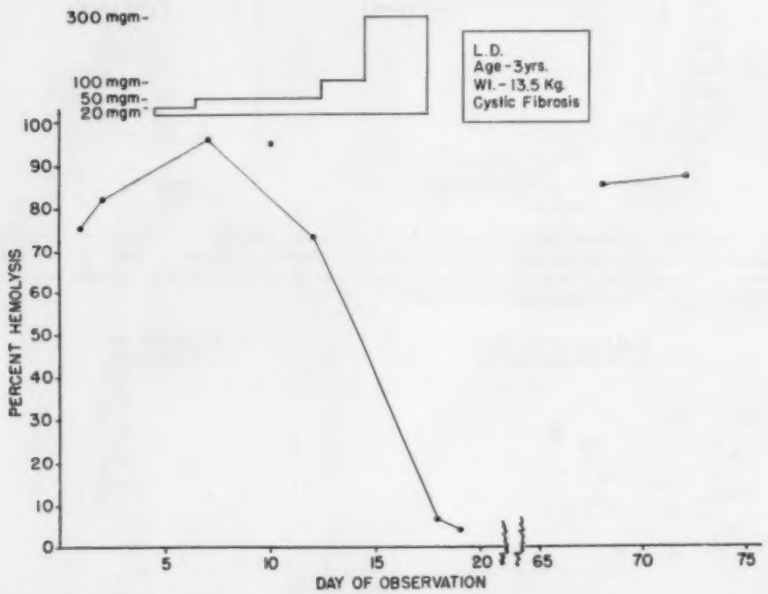

Fig. 5.—Effect of tocopherol supplementation on hemolysis in hydrogen peroxide of erythrocytes of a 3-year-old child with cystic fibrosis of the pancreas. Seven weeks after ingestion of 1440 mg. of tocopherol acetate the tests had become markedly positive again in this child, who died because of continuing pulmonary infection.

(5) *Infants and Children with Various Diseases.*—Two children with diabetes mellitus, one with galactosemia, one with recurrent hypoglycemia, three with cretinism, one with pseudohypertrophic muscular dystrophy, two with Hand-Schüller-Christian syndrome, two with Gaucher's disease, one with chronic hepatitis, one with portal hypertension, one with rheumatoid arthritis, and one suspected of "collagen disease" were studied. None showed hemolysis above 4%.

Five children with leukemia, one with aplastic anemia, one with thalassemia, two with sickle-cell anemia, one with hemolytic anemia probably due to sulfonamide, and one with anemia secondary to chronic blood loss were studied. All showed hemolysis below 8%, with the exception of the patient with aplastic anemia (16%) and one leukemic child who on the day before death showed 50% hemolysis.

COMMENT

The finding[17] that the erythrocytes of many prematurely born infants showed more hemolysis in hydrogen peroxide during the early weeks of life than had been reported for

newly born term infants [15] led to consideration of the relative importance of maturity and diet. The similarity of the values for hemolysis in newly born, unfed, term, and premature infants indicates that maturity is not the deciding factor. This is supported by the findings on serum levels [10] and tissue concentrations of tocopherol in such infants.‖ The increasing hemolysis of erythrocytes (Table 4 and Fig. 2) and the decreasing serum tocopherol [9] of premature infants with increasing duration of low-tocopherol diets indicate, on the other hand, the importance of dietary intake.

Additional evidence is noted if one arranges the infants in groups according to estimated tocopherol content of the diets.¶

TABLE 5.—*Distribution of Hemolysis Tests of Thriving Young Infants in Relation to Estimated Tocopherol Content of Diet*

Infants	No.	Type Diet	Estimated Tocopherol Content,* Mg./100 Cc.	Observations with Hemolysis, per Cent		
				<10%	11%-50%	>50%
Premature						
Negro	53	Partially skimmed cows'-milk mixture	0.04	6	35	59
White	84			7	26	67
Term						
Negro	25	Evaporated-milk mixture	0.10	22	44	34
White	29			55	31	14
Termf	18	Breast-fed	0.25	83	11	6

* References 9 and 27.
† Seven infants were white and eleven Negro.

Of 18 infants fed at the breast, 15, or 83%, showed less than 10% hemolysis, whereas only 6%-7% of the infants fed partially skimmed cows'-milk mixtures has this low level of hemolysis. The uniform effectiveness of oral *dl*-α-tocopherol acetate in reversing hemolysis is direct evidence of the relationship.

A possible influence of maternal diet is suggested grossly by the findings of a lower mean hemolysis value among infants born to mothers on the private service as compared to those born on the public service, and among white as compared to Negro infants. Since no dietary surveys were made in any of the mothers, this in only surmise; estimated differences in tocopherol content of unsupplemented diets of pregnant women apparently lead to only slight, if any differences in maternal serum concentrations.[28]

If one accepts the data cited on serum tocopherol concentrations and hemolysis of erythrocytes in hydrogen peroxide as evidence of tocopherol deficiency, one may ask whether to attempt to reverse these findings by administration of tocopherol. This may be discussed in relation to two groups of subjects, the young infants and the infants and children with steatorrhea.

In the former, positive hemolysis tests were found in both premature and term infants, and these were easily reversed in the premature infants by addition of tocopherol supplements and in the full-term infants by breast-feeding and less regularly by cows'-milk mixtures. The findings have led György to suggest the existence of a "physiologic deficiency in the newborn," [29] a situation comparable to that with respect to vitamin K. Mason has asked "whether the seemingly precarious tocopherol status of the newborn infant provides any basis for a natural or conditioned deficiency state during infancy or childhood." [30]

Evidence that this deficiency is of clinical importance to the newborn infant is difficult to establish. However, various conditions associated with vitamin E restriction in animals and certain clinical states in newborn infants suggest that this deficiency may be significant in humans. The vascular stasis and hemorrhages seen in the fetus of the rat under conditions of moderate vitamin E restriction,# the hemorrhagic manifesta-

‖ References 25 and 26.

¶ References 9 and 27.

References 31 and 32.

tions in the E-deficient chick embryo,* the subcutaneous, pulmonary, and cerebral edema of young E-deficient chickens,† and hemorrhages into cranium, lungs, and visceral cavities of puppies born to E-deficient mothers [37] are all sufficiently suggestive of commonly observed clinical and pathological findings in premature infants to warrant note. Minkowski [38] has reported increased resistance of the small vessels of premature infants of mothers given tocopherol as compared with those of untreated mothers. He also noted an effect on vascular resistance and dilatation when tocopherol was given to premature infants. In view of the seriousness for premature infants of the pathological manifestations of increased capillary permeability in the neonatal period, these findings merit attempts at confirmation. Increase of tocopherol concentrations in the infant by administration to the mother is, however, more difficult than in the analogous situation in which one can influence the prothrombin clotting time of the infant by administration of vitamin K to the mother.

Edema in premature infants, a less urgent clinical sign, may be partly dependent on increased capillary permeability. It is seen in some premature infants at birth both with complications of pregnancy, particularly diabetes mellitus, and without them. Gerloczy cited dramatic clearing of scleredema in premature infants following administration of tocopherol, but in a later report withdrew this conclusion.‡ Haziness of the vitreous has been reported on ophthalmoscopic examination of very young premature infants,[39] a finding which may represent seepage from retinal vessels. In older premature infants, edema is occasionally seen. It is usually, although not always, associated with an increase in ingestion of electrolytes, as on abrupt change from human to cows' milk § or overfeeding with cows' milk, particularly with added sodium chloride.[43] In the former instance, it has been, in our experience, transitory; its irregular occurrence probably makes it unsuitable as a quantitative sign for studying its relation to tocopherol deficiency.

Fetal hemoglobin has been reported to disappear more quickly from the blood of premature than of full-term infants [44] and fetal red cells to have a shorter survival time than adult cells.[45] Although the instability of free peroxides casts doubt on their importance in normal metabolic processes, it is possible that prolonged tocopherol deficiency may contribute to the decreased red cell survival reported in premature infants and thus indirectly to the anemia of prematurity when the ability to synthesize adult hemoglobin is not yet adequate. To the extent that the change from partial oxygen saturations of fetal blood while in utero to the higher saturations of extrauterine existence contributes to postnatal hemolysis, an antioxidant like tocopherol might offer some protective value. No evidence is available for this surmise.

As already mentioned, the positive hemolysis tests in both full-term and premature infants were easily reversed, in the former by feeding of breast-milk or even cows'-milk diets, in the latter by supplementation with small doses of tocopherol acetate. For the infants and children with steatorrhea, there was, however, much more difficulty in obtaining reversal of the test, even though in vitro addition of tocopherol to their erythrocytes produced a reversal. The evidence suggests that these subjects suffer from a more prolonged and intense deficiency, as might have been expected from the reports on serum tocopherol levels in patients with sprue ‖ and in infants and children such as those herein reported.[24] Surgical production of a biliary fistula leads to vitamin-E deficiency in the rat [48] and dog,[49] and deposition of acid-fast ceroid pigment, a manifestation of E deficiency, has been reported in patients with absorptive defects.¶ It would therefore seem reasonable to try to find some clinical,

* References 33 and 34.

† References 35 and 36.

‡ Gerloczy, F.: Paediat. Danub. **6**:83, 1949, cited by Mason.[50]

§ References 40-43.

‖ References 46 and 47.

¶ References 50 and 51.

physiological, or biochemical correlates of E deficiency in these subjects.

In the absence of such findings, one is left with uncertainty as to whether to recommend tocopherol supplementation of the diets of premature infants fed partially skimmed cows'-milk mixtures or of full-term infants fed whole cows'-milk mixtures. That the infants were apparently thriving when their hemolysis tests were positive is not an absolute argument against the need of supplementation; premature infants in whom hydroxyphenyluria was found as an early manifestation of ascorbic-acid deficiency showed no roentgen or clinical evidence of scurvy.[52] If one could definitely relate some biochemical, physiologic, or pathologic finding to E deficiency in humans one could not only recommend routine supplementation of the diets of artificially fed infants but also point to a nutritional superiority for breast feeding.

SUMMARY

Observations are made of the hemolysis of erythrocytes in hydrogen peroxide in the following groups of infants and children: unfed newborn, 282 term and 67 premature infants; thriving young term, 72, and premature, 137 infants; young term infants admitted to the hospital for various illnesses, 34 observations on 17 infants; malnourished infants and children, 38 observations in 21 subjects with steatorrhea and 21 in subjects of comparable age but without steatorrhea; infants and children with a variety of less common diseases, 27.

From 25% to 56% of unfed newborn infants in different categories showed over 50% hemolysis. No significant differences were found between full-term and premature, but the proportions of infants with over 50% hemolysis and the mean per cent hemolysis appeared to vary inversely with the economic status of the mothers. Thriving full-term infants fed cows' milk showed significantly less hemolysis at average age 7 weeks than at birth. Eighteen infants who were breast-fed showed still less hemolysis at the same average age. On the other hand, premature infants fed partially skimmed cows'-milk mixtures showed an increasing, or maintained, hemolysis with increasing duration of the low-tocopherol intake. Full-term infants admitted to the hospital for illness and given low-fat diets showed over 50% hemolysis in two-thirds of the observations.

The administration of *dl*-α-tocopherol acetate to 23 premature and 8 full-term infants led to prompt reversal of the test in every instance, even when doses as low as 1 mg/kg. daily were given.

Infants and children with steatorrhea (cystic fibrosis of the pancreas, celiac syndrome, biliary obstruction, familial steatorrhea) showed marked susceptibility of their red blood cells to hydrogen peroxide. This could be reversed either by feeding large amounts of tocopherol acetate or by addition of tocopherol in vitro. In the infants with biliary atresia, reversal of the test by feeding tocopherol was particularly difficult.

None of the infants or children with the less common diseases (diabetes mellitus, two; hypoglycemia, one; galactosemia, one; cretinism, three; xanthomatoses, four; chronic hepatitis, one; portal hypertension, one; rheumatoid arthritis, one; "collagen disease," one; pseudohypertrophic muscular dystrophy, one; leukemia, five; thalassemia, one; sickle-cell anemia, two; aplastic anemia, one; hemolytic anemia due to sulfonamide, one; anemia due to blood loss, one) showed significant hemolysis except for one leukemic child on the day before death.

The desirability of supplementing the diets of artificially fed infants with tocopherol is discussed, and no conclusions are reached because of the difficulty in assessing the significance of the dietary deficiency indicated by the hydrogen peroxide hemolysis test.

REFERENCES

1. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants: II. Studies on the Prophylaxis of the Disease; The use of Alpha Tocopheryl Acetate, Am. J. Ophth. **32**:1631, 1949.

2. Rubner, M., and Langstein, L.: Energie-und Stoffwechsel zweier frühgeborener Säuglinge, Arch. Physiol. **39**:39, 1915.

3. Muhl, G.: Fat Absorption and Calcium Metabolism of Prematurely Born Infants, Acta pædiat. **5**:188, 1926.

4. Tidwell, H. C.; Holt, L. E., Jr.; Farrow, H. L., and Neale, S.: II. Fat Absorption in Premature Infants and Twins, J. Pediat. **6**:481, 1935.

5. Gordon, H. H., and McNamara, H.: Fat Excretion of Premature Infants: I. Effect on Fecal Fat of Decreasing Fat Intake, Am. J. Dis. Child **62**:328, 1941.

6. Morales, S.; Chung, A. W.; Lewis, J. M.; Messina, A., and Holt, L. E., Jr.: Absorption of Fat and Vitamin A in Premature Infants: Effect of Different Levels of Fat Intake on the Retention of Fat and Vitamin A, Pediatrics **6**:86, 1950.

7. Powers, G. F.: Some Observations on the Feeding of Premature Infants Based on 20 Years' Experience at the New Haven Hospital, Pediatrics **1**:145, 1948.

8. Gordon, H. H.; Levine, S. Z., and McNamara, H.: Feeding of Premature Infants: A Comparison of Human and Cow's Milk, Am. J. Dis. Child. **73**:442, 1947.

9. Wright, S. W.; Filer, L. J., Jr., and Mason, K. E.: Vitamin E Blood Levels in Premature and Full Term Infants, Pediatrics **7**:386, 1951.

10. Moyer, W. T.: Vitamin E Levels in Term and Premature Infants, Pediatrics **6**:893, 1950.

11. Kinsey, V. E., and Chisholm, J. F., Jr.: Retrolental Fibroplasia: Evaluation of Several Changes in Dietary Supplements of Premature Infants with Respect to the Incidence of the Disease, Am. J. Ophth. **34**:1259, 1951.

12. György, P., and Rose, C. S.: Effect of Dietary Factors on Early Mortality and Hemoglobinuria in Rats Following Administration of Alloxan, Science **108**:716, 1948.

13. Rose, C. S., and György, P.: Hemolysis with Alloxan and Alloxan-like Compounds and the Protective Action of Tocopherol, Blood **5**:1062, 1950.

14. Rose, C. S., and György, P.: Specificity of Hemolytic Reaction in Vitamin E-Deficient Erythrocytes, Am. J. Physiol. **168**:414, 1952.

15. György, P.; Cogan, G., and Rose, C. S.: Availability of Vitamin E in the Newborn Infant, Proc. Soc. Exper. Biol. & Med. **81**:536, 1952.

16. Cohen, S.; De Metry, J. P., and Herrmann, H.: Resistance of Red Cells to Dialuric Acid of Premature Infants with Retrolental Fibroplasia, Proc. Soc. Exper. Biol. & Med. **77**:134, 1951.

17. Gordon, H. H., and De Metry, J. P.: Hemolysis in Hydrogen Peroxide of Erythrocytes of Premature Infants: Effect of Alpha-Tocopherol, Proc. Soc. Exper. Biol. & Med. **79**:446, 1952.

18. Gordon, H. H.: The Relation of Vitamin E to Hemolysis of Erythrocytes in Hydrogen Peroxide: Prematurity, Congenital Malformation and Birth Injury. Proceedings of Conference of Association for The Aid of Crippled Children, New York, June, 1952.

19. Mackenzie, J. B.: Relation Between Serum Tocopherol and Hemolysis in Hydrogen Peroxide of Erythrocytes in Premature Infants, Pediatrics **13**:346, 1954.

20. Gordon, H. H.; Davis, R. H., and Morganstein, K.: Effect of Alpha-Tocopherol on Hemolysis of Erythrocytes in Hydrogen Peroxide, Fed. Proc. **12**:415, 1953.

21. Quaife, M. L.: Tocopherols (Vitamin E) in Milk: Their Chemical Determination and Occurrence in Human Milk, J. Biol. Chem. **169**:513, 1947.

22. Abderhalden, R.: Der Vitamin E-Gehalt der Frauen-und kuhlmilch, Biochem. Ztschr. **318**:47, 1947.

23. Rauramo, L.: Sur le Dosage du tocophérol (vitamine E) dans le sérum sanguin et le lait, et sur la teneur du sérum en tocophérol particulièrment pendant la grossesse et la période de l'allaitement, Acta obst. et gynec. Scandinav. (Supp. 2) **27**:1, 1947.

24. Filer, L. J.; Wright, S. W.; Manning, M. P., and Mason, K. E.: Absorption of α-Tocopherol and Tocopheryl Esters by Premature and Full Term Infants and Children in Health and Disease, Pediatrics **8**:328, 1951.

25. Dju, M. Y.; Mason, K. E., and Filer, L. J., Jr.: Vitamin E (Tocopherol) in Human Fetuses and Placentae, Etudes Neonatal. **1**:49, 1952.

26. Abderhalden, R.: Der tokopherolgehalt in den organen von menschlichen fõten und neugeborenen. Internat. Ztschr. Vitamin forsch. **16**:319, 1945.

27. Harris, P. L.; Quaife, M. L., and O'Grady, P.: Tocopherol Content of Human Milk and of Cows' Milk Products Used for Infant Feeding, J. Nutrition **46**:459, 1952.

28. Ferguson, M. E.; Bridgeforth, E.; Quaife, M. L.; Martin, M. P.; Cannon, R. O.; McGanity, W. J.; Newbill, J., and Darby, W. J.: The Vanderbilt Cooperative Study of Maternal and Infant Nutrition: VIII. Tocopherol in Relation to Pregnancy, J. Nutrition **55**:305, 1955.

29. György, P.: Vitamins—Past and Present, Pediatrics **15**:119, 1955.

30. Mason, K. E.: The Tocopherols: VII. Effect of Deficiency, in the Vitamins, Chemistry, Physiology, Pathology, edited by W. H. Sebrell Jr., and R. S. Harris, New York, Academic Press, Inc., 1954, Vol. 3, p. 514.

31. Mason, K. E.: Changing Concepts of the Antisterility Vitamin (Vitamin E), Yale J. Biol. & Med. **14**:605, 1942.

32. Mason, K. E.: A Hemorrhagic State in the Vitamin E-Deficient Fetus of the Rat, in Evans, H. M.: Essays in Biology in Honor of H. M. Evans: Written by His Friends, Berkeley, Calif., University of California Press, 1943, p. 401.

33. Adamstone, F. B.: The Effect of Vitamin E Deficiency on the Development of the Chick, J. Morphol. **52**:47, 1931.

34. Adamstone, F. B.: Histologic Evidence Indicative of the Nature Occurrence of Vitamin E Deficiency in the Chick, Arch. Path. **31**:622, 1941.

35. Dam, H., and Glavind, J.: Alimentary Exudative Diathesis and Its Relation to Vitamin E, Skandinav. Arch. Physiol. **82**:299, 1939.

36. Bird, H. R., and Culton, T. G.: Generalized Edema in Chicks Prevented by *d,l*-Alpha Tocopherol, Proc. Soc. Exper. Biol. & Med. **44**:543, 1940.

37. Elvehjem, C. A.; Gonce, J. E., Jr., and Newell, G. W.: The Effect of Vitamin E on Reproduction in Dogs on Milk Diets, J. Pediat. **24**:436, 1944.

38. Minkowski, A.: L'atteinte des petits vaisseaux au cours des hémorragies néo-natales: Limites d'action de la vitamine K; Rôle possible de la fragilité vasculaire; Intér de la capillaroscopie, Sang **22**:701, 1951.

39. Guy, L. P.; Dancis, J., and Lanman, J. T.: Retrolental Fibroplasia: Ophthalmoscopic Findings During the First 2 Weeks of Life, Am. J. Ophth. **36**:85, 1953.

40. Gordon, H. H.; Harrison, H. E., and McNamara, H.: Urea Clearance of Young Premature and Full Term Infants, J. Clin. Invest. **21**:499, 1942.

41. Beem, M., and Smith, C. A.: Response of Premature Infants to Dietary Changes, read before The Society for Pediatric Research, May 6, 1952.

42. Kagan, B. M.; Hess, J. H.; Lundeen, E.; Shafer, K.; Parker, J. B., and Stigall, C.: Feeding Premature Infants: A Comparison of Various Milks, Pediatrics **15**:373, 1955.

43. Hepner, W. R., Jr., and Krause, A. C.: Retrolental Fibroplasia: Clinical Observations, Pediatrics **10**:433, 1952.

44. Schulman, I.; Smith, C. H., and Stern, G. S.: Studies on the Anemia of Prematurity: I. Fetal and Adult Hemoglobin in Premature Infants, A. M. A. Am. J. Dis. Child. **88**:568, 1954.

45. Hollingsworth, J. W.: Lifespan of Fetal Erythrocytes, J. Lab. & Clin. Med. **45**:469, 1955.

46. Darby, W. J.; Cherrington, M. E., and Ruffin, J. M.: Plasma Tocopherol Levels in Sprue, Proc. Soc. Exper. Biol. & Med. **63**:310, 1946.

47. Darby, W. J.; Jones, E.; Warden, H. F., and Kaser, M. M.: The Influence of Pteroylglutamic Acid (Member of Vitamin M Group) on Gastrointestinal Defects in Sprue: A Study of Interrelationships of Dietary Essentials, J. Nutrition **34**: 645, 1947.

48. Greaves, J. D., and Schmidt, C. L. A.: Relation of Bile to Absorption of Vitamin E in the Rat, Proc. Soc. Exper. Biol. & Med. **37**:40, 1937.

49. Brinkhaus, K. M., and Warner, E. D.: Muscular Dystrophy in Biliary Fistula Dogs: Possible Relation to Vitamin E Deficiency, Am. J. Path. **17**: 81, 1941.

50. Pappenheimer, A. M., and Victor, J.: "Ceroid" Pigment in Human Tissues, Am. J. Path. **22**:395, 1946.

51. Tverdy, G.; Froehlich, A.-L., and Fierens, B.: L'avitaminose E au cours de la sprue, Acta gastroenterol. belg. **12**:221, 1949.

52. Levine, S. Z.; Gordon, H. H., and Marples, E.: Defect in Metabolism of Tyrosine and Phenylalanine in Premature Infants: Spontaneous Occurrence and Eradication by Vitamin C, J. Clin. Invest. **20**:209, 1941.

News and Comment

ANNOUNCEMENTS

A. M. A. Annual Meeting, Chicago, June 11-15, 1956.—The 105th Annual Meeting of the American Medical Association will be held in Chicago, June 11-15, 1956, with a full program of lectures, television, motion pictures, and scientific exhibits.

The lecture program for each Section is prepared by the Section Secretary, and prospective participants should communicate as soon as possible with the Secretary of the Section before which they hope to read a paper. Application blanks for space in the Scientific Exhibit are now available and may be obtained from the Section Representative to the Scientific Exhibit.

Section on Pediatrics

Secretary: Wyman C. C. Cole Sr., M.D., 3001 W. Grand Blvd., Detroit 2.

Exhibit Representative: F. Thomas Mitchell, M.D., Le Bonheur Children's Hospital, Memphis 5.

Additional information may be obtained from the Secretary, Council on Scientific Assembly, American Medical Association, 535 N. Dearborn St., Chicago 10.

Studies in Sickle-Cell Anemia

VIII. Further Observations on the Clinical Manifestations of Sickle-Cell Anemia in Children

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INTRODUCTION

Genetically, sickle-cell anemia was probably first introduced into the United States in 1619, when the first African slaves were brought to the colonies. The initial clinical description was recorded by Herrick in 1910.[1] The asymptomatic trait has been found to occur in 7% to 10% of Negroes in this country.[2] Sickle-cell anemia fortunately is much less prevalent; it is estimated that between 30,000 and 100,000 individuals suffer from this disease in the United States.[3]

It is now generally accepted that the gene responsible for sickling produces the asymptomatic trait when present in the heterozygous state [4] and active sickle-cell disease when it occurs in the homozygous state.

The red blood cells in both sickle-cell anemia and the sickling trait contain an abnormal hemoglobin ("S" hemoglobin) and are capable of distorting their shape when exposed to reduced oxygen tension. The red blood cells in persons with the asymptomatic sickling trait contain two types of hemoglobin, namely, the normal adult variety (55%-76%) and the sickle-cell hemoglobin (24%-45%).[5] The extent of in vivo sickling in the trait condition is less than 1%,[6] hence, there are no clinical symptoms and no indication for treatment under ordinary circumstances. On the other hand, in sickle-cell anemia, where 30% to 60% of the erythrocytes in the venous circulation are sickled and where 75% to 100% of the hemoglobin is of the abnormal "S" type, a variety of symptoms may occur.

In sickle-cell anemia, the distorted erythrocytes have a shortened life span and are destined for premature destruction, with a resulting hemolytic disease. The morbid characteristics of the disease can be attributed to both intrinsic and extrinsic factors. Among the former may be listed intravascular sickling, excessive red blood cell hemolysis, anemia, increased blood viscosity, capillary blockade, infarcts, thrombi, and ischemic necrosis. Extrinsic and precipitating factors of particular importance during childhood are periods of rapid growth and certain stress conditions, such as infections, trauma, and dehydration.

In general, the character of the symptoms in the individual patient depends mainly upon the severity of the anemia and the site of organ involvement. The disease is of particular importance to the physician caring for children because the onset of first symptoms usually occurs during the preschool period.[7]

This presentation deals with the clinical manifestation of sickle-cell anemia in 63 Negro children. Special emphasis is centered upon the natural course of the disease with reference to different age groups from infancy to adolescence. The children ranged in age from 3 months to 15 years and represented 401 hospital admissions from 1940 to 1954. The mean age at first admission

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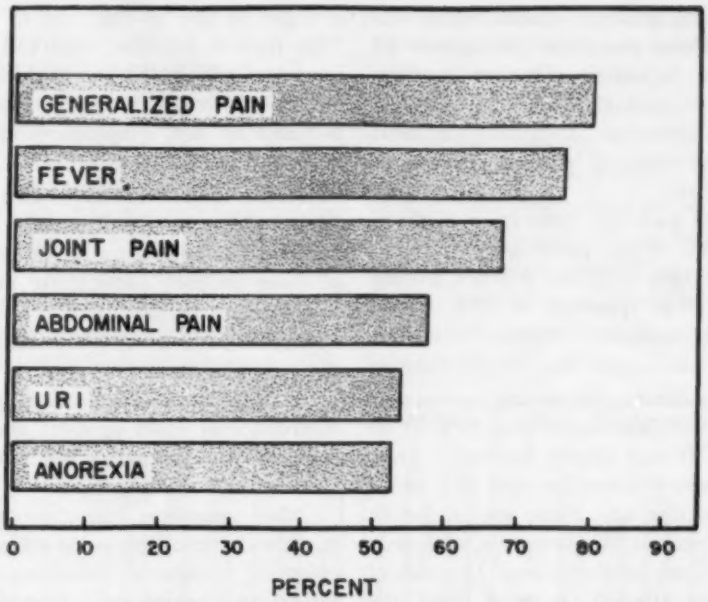

Fig. 1.—Per cent of admissions reporting six main symptoms. Some admissions are entered more than once because of multiple complaints (63 children with sickle-cell anemia admitted 401 times over a period of several years).

to the hospital was 4.7 years. There were 39 boys and 24 girls.

SYMPTOMATOLOGY

The protean symptomatology of sickle-cell anemia is well known. The most frequent complaints encountered in this series were pain, fever, upper-respiratory-tract infections, and anorexia (Fig. 1). Our experience with certain aspects of symptomatology is further described in Figure 2.

1. *Pain.*—Generalized pain was the commonest presenting symptom and was elicited

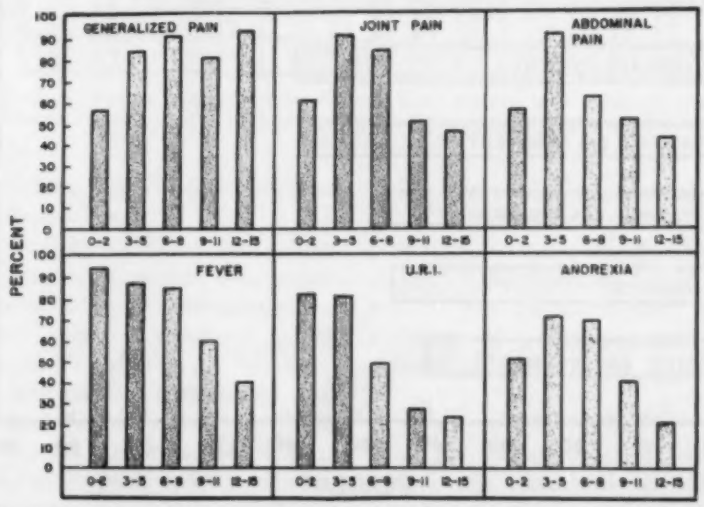

Fig. 2.—Age relations of main complaints on admission of 63 patients with sickle-cell anemia from infancy through 15 years of age. Each bar represents the per cent of admissions with the specified symptom in a three-year age group.

in 80% of the patients studied. Pain was a fairly uniform complaint throughout all age periods. Arthralgia alone or in combination with pain elsewhere appeared in 68% of the admissions. Joint pain was most frequently encountered between the ages of 2 and 10 years.

Abdominal pain was present in 57% of all admissions. It was particularly prevalent between the ages of 2 and 8 years, during which period it appeared in 75% of all children. Chronologically, it then declined in frequency.

2. *Fever.*—Fever, the second commonest complaint, was observed in over 76% of all admissions. It was almost invariably present in children between the ages of 1 and 9 years. After this age, there was a decline in the incidence of this symptom, with only 33% of patients admitted over 13 years of age being so affected. In most cases, the elevated temperature could be readily attributed to an associated infection.

3. *Respiratory Tract Infections.*—Infections in the upper respiratory tract were found in over 70% of the children under 6 years of age at the time of admission. This type of infection apparently plays an important role in the precipitation of sickle-cell anemia crises in young children. After 6 years of age, respiratory infections in these patients were less prevalent.

4. *Anorexia.*—We have been impressed for some time with the frequency with which anorexia has been encountered on admission of these patients, particularly in the 2- to 8-year age period. This complaint was elicited in 53% of all admissions. We have observed that anorexia, even in the absence of a demonstrable infection, is often a forerunner of crisis episodes and may precede for days or weeks the more dramatic onset of pain.

Other symptoms less commonly encountered in children with sickle-cell anemia were epistaxis, headache, vomiting, weakness, fatigability, convulsions, irritability, shock, somnolence, listlessness, and myalgia.

PHYSICAL FINDINGS

The physical findings in sickle-cell anemia may present considerable variation in indi-

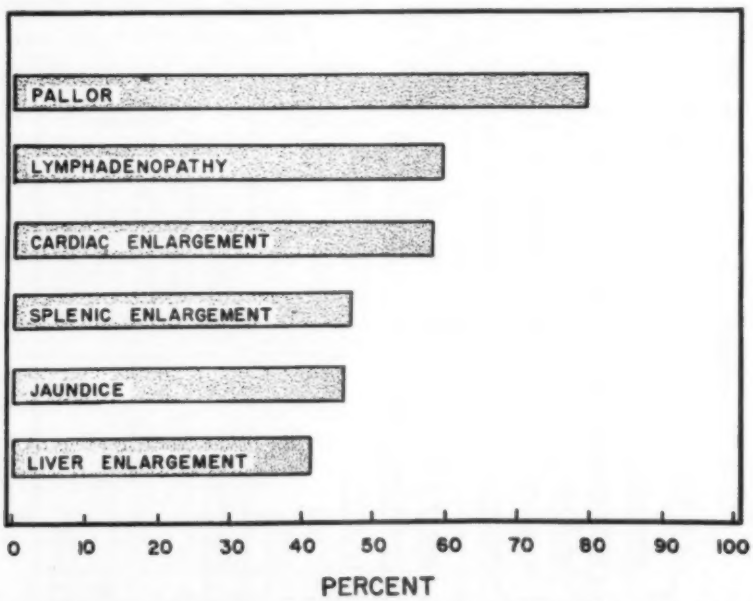

Fig. 3.—Per cent of admissions showing six main physical signs, which were elicited at the time of hospitalization (63 children with sickle-cell anemia admitted 401 times over a period of several years).

vidual cases. On the basis of our experience, the most commonly observed findings may be summarized as follows (Figs. 3, 4).

(1) Pallor: Some degree of mucosal or cutaneous pallor was noted in 80% of the admissions. This finding, which is best elicited in Negroes in the conjunctival or buccal mucosa and in the nail beds, palms, and soles, was fairly evenly distributed throughout the first 12 years of life.

(2) Lymphadenopathy: Palpable lymph nodes—cervical, submaxillary, axillary, epitrochlear, or inguinal—were present in 60% of the admissions, with a peak incidence during middle childhood.

(3) Cardiomegaly: Of the total admissions, 58% presented cardiac enlargement demonstrable either by physical examination and/or x-ray. This is a consistent finding after the second year of life.

(4) Splenomegaly: Splenomegaly was found in 47% of the total admissions. Below the age of 6 years, approximately 60% of the children had palpable spleens, whereas after 6 years of age, the spleen was palpated in less than 50% of the admissions.

(5) Jaundice: As a physical finding, jaundice was present in about 30% of the children under 4 years of age, whereas after this age, it tended to increase to a level of about 50% incidence.

(6) Hepatic enlargement: Some degree of liver enlargement was found throughout the first 11 years, with a peak incidence between 3 and 9 years. There was no apparent correlation between the degree of hepatic enlargement and the appearance of jaundice by physical examination.

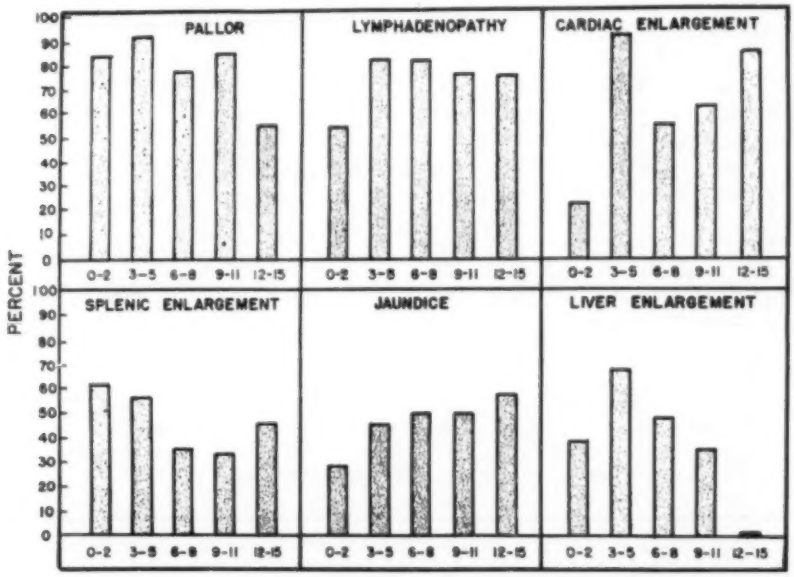

Fig. 4.—Age relations of main physical findings in 63 patients with sickle-cell anemia from infancy through 15 years of age. Each bar represents the per cent of admissions for a three-year age group.

(7) Other findings somewhat less frequently encountered were cardiac murmurs, poor nutrition and asthenic habitus, lordosis, ascites, joint swelling, hemiplegia, osteoporosis, and gallstones. Only one patient, a 14-year-old boy, presented a chronic cutaneous ulcer of the leg.

LABORATORY DATA

A provisional diagnosis of sickle-cell anemia can oftentimes be inferred from examination of the stained blood smear, which may reveal sickled forms, anisocytosis,

poikilocytosis, polychromatophilia, and target cells. The finding of sickled erythrocytes on a stained dry blood smear practically never occurs in the simple trait state; hence their presence under these circumstances indicates sickle-cell anemia as a rule.

For routine diagnostic screening of new patients, we employ moist unstained specimens prepared by mixing one drop each of freshly drawn blood and 2% solution of sodium metabisulfite. By use of this simple technique, microscopic sickling can be elicited in 5 to 15 minutes.

and hospital observations) except for a rise after the ninth year of life.

The total leucocyte count (mean 16,848 cells per cubic millimeter) was consistently higher than that found in normal children. The leucocytosis in one child with a complicating infection was 76,400 cells per cubic millimeter.

In a group of patients studied with particular reference to the reticulocyte response, 51 observations showed the reticulocyte count to range from 0% to 30%, with a mean value of 1.4%. In another study group,

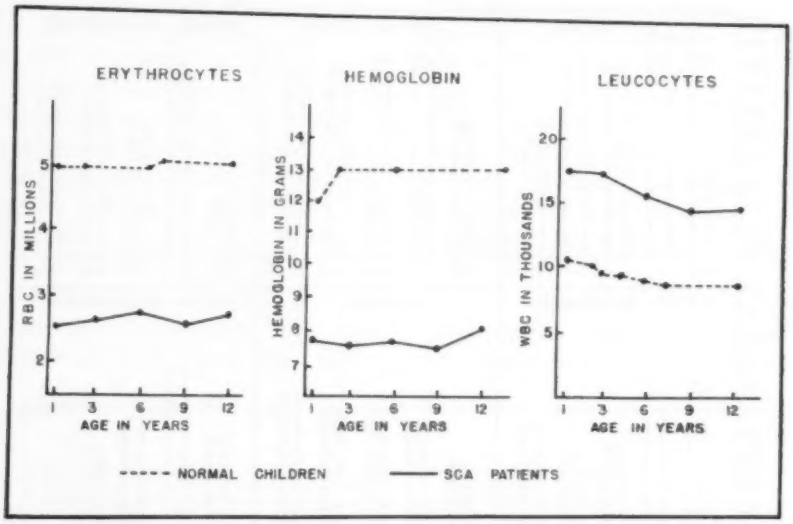

Fig. 5.—Age data on hematologic characteristics of 63 sickle-cell-anemia patients compared with normal children (values for normal children obtained from Wolman, I. J.: The Peripheral Blood Count of Children, *J. Nat. M. A.* **47**:1-12 (Jan.) 1955).

Paper electrophoresis is of value in certain instances for the differentiation of the disease from the trait. It is also essential for the identification of certain abnormal hemoglobins which are found in other hemolytic syndromes.[8]

The mean erythrocyte count (782 clinic and hospital observations) in our subjects was 2,600,000 per cubic millimeter (Fig. 5). This level was fairly constant throughout the first 13 years of life and appears to represent the "adjusted physiological norm" for these children. Similarly, the hemoglobin concentration varied only very slightly from the mean of 7.7 gm. per 100 cc. (918 clinic

the mean value for the indirect van den Bergh test was 1.7 units for children under 5 years of age (22 observations) and 4.9 units after this age (32 observations).

Two uniformly consistent findings in these patients were increased resistance of the erythrocytes to hypotonic saline solutions and impaired ability to concentrate urine. The mean specific gravity of the urine observed in this series was 1.012. The fixation of specific gravity is manifested even in very young children and is attributed by some investigators to renal tubular dysfunction. The total plasma protein and A/G ratios were within normal range.

TABLE 1.—*Diseases and Symptoms Easily Confused with Sickle-Cell Anemia*

Diseases	Symptoms and Signs
Other anemias Rheumatic fever, carditis, and other rheumatoid states Infectious hepatitis	Anorexia Arthralgia Abdominal pain Cardiac enlargement Cardiac murmur Fever Jaundice Joint swelling Liver enlargement Pallor Generalized pain
Meningitis Poliomyelitis	Convulsions Delirium or disorientation Paralyses Prostration Stiff neck, stiff back Malaise Vomiting Myalgia Coma Fever
Nephritis	Low fixed specific gravity Albuminuria Hypertension Hematuria Casts in urine
Acute "surgical" abdomen	Abdominal pain Nausea and vomiting Fever
Osteomyelitis Leukemia Bacterial endocarditis	Joint swelling Bone tenderness Fever Leucocytosis Anemia Enlarged spleen

DIFFERENTIAL DIAGNOSIS

Sickle-cell anemia may mimic many other conditions and has been called "a great masquerader."[8] Perhaps one of the commonest clinical errors is to confuse this hemolytic disease with the asymptomatic sickling trait (sicklemia). Such confusion is most likely to occur when the individual bearing the sickling trait acquires another condition, such as nutritional anemia, or a disease like infectious hepatitis or rheumatic fever. In our experience, the diseases and symptoms which are most likely to be confused with sickle-cell anemia are those shown in Table 1.

TREATMENT

Since there is no specific or curative treatment for sickle-cell anemia, a wide variety of agents have been used. The more commonly employed therapeutic procedures and their indications are listed in Table 2. The disease is characterized by periods of remission and exacerbation.

Therapy in childhood is directed chiefly toward control of clinical crises. At the present time, transfusions of whole blood or packed red blood cells represent the most dependable method of combating pain, shock, debility, and severe grades of anemia. Mild crises characterized by slight or transient pain may occasionally respond satisfactorily to bed rest and sedatives or analgesics.

Anemia per se, particularly during periods of quiescence, is not an indication for blood transfusion, because these children learn to lead fairly active lives despite a hemoglobin concentration of 7 or 8 gm. per 100 cc.

In recent years, it has been our policy in general to reserve blood transfusions in these patients for the following conditions:

1. Severe crisis associated with debility, excruciating pain, and marked anemia
2. Presence of formidable complicating infections, such as pneumonia, meningitis, septicemia
3. In selected cases, for elective or emergency surgical operations
4. When other medical measures have failed to control the crisis.

TABLE 2.—*Summary of Some of the Agents Used in the Treatment of Sickle-Cell Anemia in Childhood*

Agent	Indication
Replacement of cellular or plasma volumes 1. Whole blood 2. Packed RBC 3. Plasma 4. Dextran 5. Water orally 6. Dextrose intravenously	Crisis, shock
Analgesics 1. Acetylsalicylic acid 2. Codeine, etc.	Pain
Vasodilators 1. Tolazoline (Priscoline), etc.	Pain
Antibiotics	Infection
Chemotherapy	Infection
Oxygen (intranasal)	Crisis, shock
Hormones 1. Cortisone 2. Corticotropin (ACTH)	Crisis, shock
Bed rest	Crisis, shock
Mental hygiene 1. Patient 2. Family	Chronic, incurable disease; feelings of guilt; feelings of inferiority
Surgery 1. Splenectomy	Extra corpuscular hemolytic factor "hypersplenism"
2. T and A	Chronic tonsillitis
3. Cholecystectomy	Cholelithiasis
Dietotherapy	Poor nutrition
Cobalt?	Anemia

The analysis of our data shows that transfusions have been most frequently required in children under 7 years of age. The increased need for blood administration in this age period is attributed to rapid body growth, frequent association of upper-respiratory-tract infections, and greater severity of the anemia in early childhood.

Prevention and prompt treatment of established intercurrent infections are important. Children with sickle-cell anemia appear to be particularly susceptible to respiratory diseases.

Because of certain undesirable features (Table 3) of multiple and repeated blood transfusions, we were encouraged to explore the efficacy of a blood substitute. Six per cent dextran with five per cent fructose was administered intravenously to nine children in crises. Five of these patients appeared to

TABLE 3.—*Hazards of Multiple Blood Transfusions*

1. Hemolytic reactions
2. Cardiac insufficiency; excess of blood
3. Bone marrow depression
4. Disease transmission
   (a) Homologous serum jaundice
   (b) Syphilis
   (c) Malaria
5. Contaminated blood—infection
6. Allergic reaction
7. Air embolism
8. Pyrogens
9. Hemosiderosis

be benefited by disappearance of pain and by increase in total hemoglobin.

Steroid hormones have been tried in selected cases. While less dependable than blood transfusion, they appear to be helpful adjuvants in the control of anorexia, debility, and pain during a hemolytic crisis.[7]

We have employed cobaltous chloride, given orally in daily doses of 2 mg. per kilogram of body weight. We observed an initial rise in reticulocytes in about four days and in hemoglobin and red blood cell counts in seven days. After 14 days of therapy, the hemoglobin and red blood cell counts reached a plateau and the reticulocytes began to decrease in number. Because of early untoward signs, such as anorexia, nausea, vomiting and rashes, and the later complication of hypothyroidism,[9] it is questionable whether cobalt can be employed safely for a chronic disease like sickle-cell anemia.

Tolayoline (Priscoline) administered both orally and parenterally to patients in crises has not been impressive in controlling pain in our experience.

We have not employed splenectomy in our series. The spleen was palpable in less than 50% of the admissions of children over 6 years of age. Splenectomy in sickle-cell anemia should be reserved for the very occasional patient who exhibits a superimposed extracorpuscular component. Such cases usually show splenomegaly with frequent crises and marked anemia which is practically refractory to multiple blood transfusions.

The management of sickle-cell anemia should include good psychologic orientation for patients and parents, because the chronicity and incurability of the disease carry a high potential for emotional trauma.

COMMENT

To date the following hemoglobins [10] have been identified in the human *:

A—normal adult hemoglobin
S—sickle-cell hemoglobin
C—C hemoglobin
D—D hemoglobin
E—E hemoglobin
F—fetal hemoglobin
G—G hemoglobin
H—H hemoglobin

Since 1954, we have employed paper electrophoresis as part of our diagnostic study on all suspected cases of sickle-cell anemia. Most of the cases in this presentation were

* Since this manuscript was prepared, at least two additional abnormal hemoglobins have been isolated (Rucknagel, D. L.; Page, E. B., and Jensen, W. N.: Hemoglobin I: An Inherited Hemoglobin Anomaly: Unpublished data; Itano, H. A.; Unpublished data; Thorup, O. A.; Itano, H. A., and Wheby, M. S.: Hemoglobin J, unpublished data; Itano, H. A.: Clinical States Associated with Alterations of the Hemoglobin Molecule, A. M. A. Int. Med. **26**:287 (Sept.) 1955.

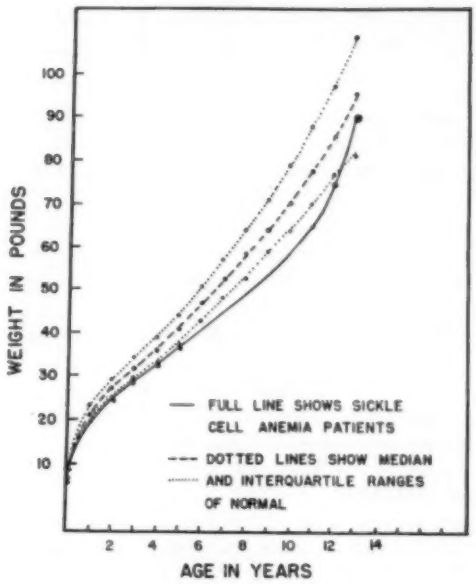

Fig. 6.—Weight curve for the 63 children in our study compared with a "normal" weight curve constructed from the median weight for boys and girls for the first 13 years of life (values for normal children obtained from Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, Ed. 5, Philadelphia, W. B. Saunders Company, 1950, pp. 60-64).

studied before electrophoresis became available as a clinical diagnostic agent. We have sought to include in this series only those cases which conformed to the clinical and hematological diagnosis of homozygous sickle-cell anemia. Many of the individual cases were followed for five to seven years.

The weight of the 63 children in this study was consistently below that of the median for normal children (Fig. 6). Many of the youngsters with sickle-cell anemia show a habitus characterized by small spindly extremities, protuberant abdomen, lordosis, and poor general nutrition.

An analysis of the seasonal distribution of admissions showed that they were fairly evenly distributed throughout the year, with a slight preponderance occurring in the spring and winter (Fig. 7).

An analysis of the 401 admissions showed that an inverse ratio existed between the chronological age of the patients and the incidence of hospital admissions (Fig. 8). This finding is attributed to the attenuating nature of the disease with increasing age of the individual.

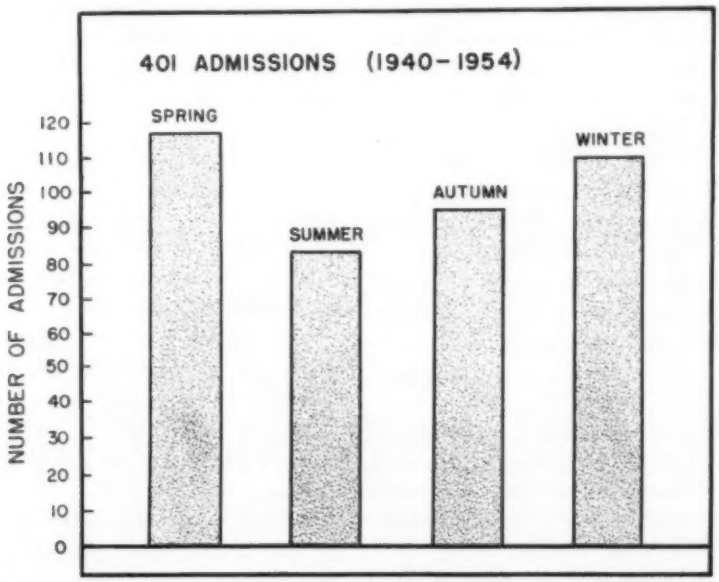

Fig. 7.—Seasonal trend in the admission of sickle-cell-anemia patients. The increased rate of admission in the winter and spring may be correlated with the prevalence of upper respiratory infections in these seasons.

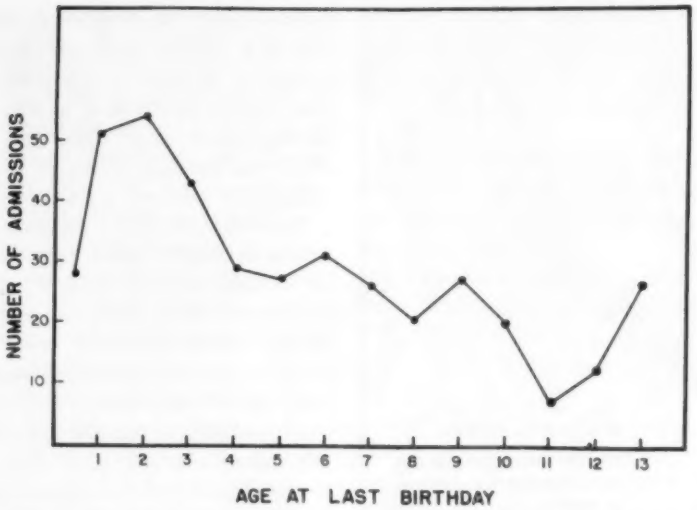

Fig. 8.—Rates by ages of 401 sickle-cell-anemia admissions. The increase in the admission rate in the early age periods is due to repeated readmission of cases in these age categories. The gradual decline in the admission rate with increasing age suggests a trend toward attenuation of the severity of the disease process with age. The average age of first admission for sickle-cell-anemia patients was 4.7 years.

Four deaths occurred during the period of observation. One patient, a 13-month-old girl, died in respiratory distress with a complicating cerebral thrombosis. A 12-year-old girl died as a result of a transfusion reaction. A third child, a 9-year-old girl, died in crisis. At the time of admission to the hospital, her hemoglobin concentration was less than 2 gm. per 100 cc. and the red blood cell count was only 730,000 cells per cubic millimeter. A fourth child, a 2-year-old girl, died soon after hospitalization for convulsions associated with hyperpyrexia. Autopsy showed pulmonary congestion and edema.

Death in children with sickle-cell anemia is most often attributed to crisis, infection, cardiac failure, and vascular accidents.

SUMMARY

The clinical manifestations of sickle-cell anemia in 63 Negro children are presented. The subjects ranged in age from 3 months to 15 years and represented 401 hospital admissions from 1940 to 1954.

The most frequently encountered complaints were pain, fever, upper-respiratory-tract infections, and anorexia. The most frequently observed physical findings were pallor, lymphadenopathy, poor nutrition, jaundice, and enlargement of the heart, liver, and spleen.

There is a tendency for certain hematologic elements to become stabilized at levels which are compatible with fairly adequate physical activity despite their variance from values commonly observed in the normal child.

Sickle-cell anemia, from the diagnostic point of view, may mimic a variety of diseases, including such dissimilar conditions as rheumatic fever, other anemias, central-nervous-system diseases, and acute "surgical" abdominal emergencies.

Although a variety of methods have been used in the management of this disease, blood transfusions together with antibacterial agents for the control of intercurrent infection remain the most reliable therapeutic agents.

Because of the chronicity and incurability of this disease, good psychological care of patients and their parents is very important.

Good medical management can do a great deal to make life more bearable for these

children. Fortunately, there is a natural tendency for the disease to become somewhat attenuated in the older child.

Dr. Leroy E. Hoeck, Chief Medical Officer in Pediatrics, District General Hospital, Washington, D. C., cooperated in making data available on several of the cases used in this study.

Dr. Bronson Price of the Children's Bureau, Washington, D. C., gave helpful suggestions in the preparation of the manuscript.

This study was supported in part by the Field Foundation, Inc., and the Mead Johnson Company.

REFERENCES

1. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517 (Nov. 15) 1910.

2. Margolies, M. P.: Sickle Cell Anemia, Composite Study and Survey, Medicine **30**:357 (Dec.) 1951.

3. Mercer, R. D.: Recent Developments in Sickle Cell Anemia, Postgrad. Med. **13**:224 (March) 1953.

4. Neel, J. V.: The Inheritance of Sickle Cell Anemia, Science **110**:64 (July 15) 1949.

5. Motulsky, A. G.; Paul, M. H., and Durrum, E. L.: Paper Electrophoresis of Abnormal Hemoglobins and Its Clinical Applications: A Simple Semiquantitative Method for the Study of the Hereditary Hemoglobinopathies, Blood **9**:897 (Sept.) 1954.

6. Pauling, L.; Itano, H. A.; Singer, S. J., and Wells, I. C.: Sickle Cell Anemia, A Molecular Disease, Science **110**:543 (Nov.) 1949.

7. Scott, R. B.; Banks, L. O.; Jenkins, M. E., and Crawford, R. P.: Studies in Sickle-Cell Anemia: II. Clinical Manifestations of Sickle-Cell Anemia in Children (An Analysis of 37 Cases with Observation on the Use of ACTH and Cortisone in 2 Additional Cases), J. Pediat. **39**:460 (Oct.) 1951.

8. Winsor, T., and Burch, G. E.: Sickle Cell Anemia, "a Great Masquerader": Easily Recognizable with Routine Use of Diagnostic Parameter, J. A. M. A. **129**:793 (Nov. 17) 1945.

9. Gross, R. T.; Kriss, J. P., and Spaet, T. H.: The Hematopoietic and Goitrogenic Effects of Cobaltous Chloride in Patients with Sickle Cell Anemia, Pediatrics **15**:284 (March) 1955.

10. A System of Nomenclature for the Varieties of Human Hemoglobin, Comments and Communications, Science **118**:116 (July 24) 1953.

11. Statement Concerning a System of Nomenclature for the Varieties of Human Hemoglobin, News and Views, Blood **8**:386 (April) 1953.

12. Itano, H. A.; Bergren, W. R., and Sturgeon, P.: Identification of a Fourth Abnormal Human Hemoglobin, J. Am. Chem. Soc. **76**:2273 (Jan. 5) 1954.

13. Chernoff, A. I.; Minnich, V., and Chongchareonsuk, S.: Hemoglobin E, a Hereditary Abnormality of Human Hemoglobin, Science **120**:605 (Oct. 15) 1954.

14. Edington, G. M., and Lehman, H.: Hæmoglobin G.: A New Hæmoglobin Found in a West African, Preliminary Communications, Lancet **2**: 173 (July 24) 1954.

15. Rigas, D. A.; Koler, R. D., and Osgood, E. A.: New Hemoglobin Possessing a Higher Electrophoretic Mobility than Normal Adult Hemoglobin Communications, Science **121**:372 (March 11) 1955.

News and Comment

ANNOUNCEMENTS

Benjamin Knox Rachford Lectureships.—The 24th annual series of the Benjamin Knox Rachford Lectureships will take place in Cincinnati, on Tuesday and Wednesday evenings, Feb. 14 and 15, 1956. Dr. Robert J. Huebner, of the National Microbiological Institute in Bethesda, Md., will deliver these lectures in the auditorium of the Children's Hospital Clinic and Research Building. The titles of his lectures are (1) "The Opportunities and Problems of Modern Virus Research" and (2) "The APC and Coxsackie Virus Infections of Childhood."

The Diagnosis of Operable Portal Obstruction in Children

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and
ALEXANDER P. REMENCHIK, M.D., Chicago

The development of surgical procedures which can modify the course of disease associated with portal hypertension has made early recognition and accurate diagnosis of this condition imperative. This applies in particular to the pediatric age group. In many cases found in infants and children such complications as hemorrhage from esophageal varices and pathological depression of erythrocyte, leucocyte, and platelet levels due to hypersplenism can be avoided by appropriate treatment. Accurate diagnosis of the cause of portal hypertension including the site of portal obstruction is necessary not only to define clearly the indications for surgery, but also to plan the most appropriate procedure.

Several extensive anatomical investigations of the portal venous system have been made recently because of the renewed interest in portal decompression in the treatment of portal hypertension.[1] A compilation of the most frequently encountered patterns in the disssections of 92 specimens by Douglass, Baggenstoss, and Hollinshead [2] of the proximal terminations of all the major veins of the extrahepatic portal system is shown in Figure 1.

Recorded for publication Aug. 15, 1955.

From the Departments of Pediatrics (Dr. Schuckmell), Surgery (Dr. Grove), and Medicine (Dr. Remenchik), University of Illinois College of Medicine, 840 S. Wood St., Chicago 12.

The pancreas is represented by the shaded area. The splenic and superior mesenteric veins join to form the portal vein just posterior to the head of the pancreas. A variable number of splenic trunks converge near the hilus to form the splenic vein. The left gastroepiploic and numerous small pancreatic branches join the splenic vein, as does usually the inferior mesenteric, which is formed by the superior hemorrhoidal and left colic veins.

The chief tributaries of the superior mesenteric vein are the intestinal, middle colic, ileocolic, right colic, omental, right gastroepiploic, and inferior pancreaticoduodenal veins. The coronary, or left gastric, vein usually terminates at the junction of the superior mesenteric and splenic veins. The superior pancreaticoduodenal; pyloric, or right gastric; cystic, and in 30% of the cases the accessory pancreatic vein enter the thick-walled portal vein.

Figure 2 shows Gilfillan's [3] statistical analysis of the morphologic variations in the portal vein and its tributaries, derived from 61 postmortem dissections. The coronary, or left gastric, vein and its accompanying pyloric vein originated from the portal vein in 68%, from the junction of the splenic and superior mesenteric veins in 8%, and from the splenic vein in 24% of cases. He found the inferior mesenteric vein entered the splenic vein in 55.6% of the cases, the junction of superior mesenteric and splenic veins in 14%, and in 29.6% of the cases drained into the superior mesenteric vein.

The first use of the term "portal hypertension" was by Gilbert,[4] in 1899. Not until

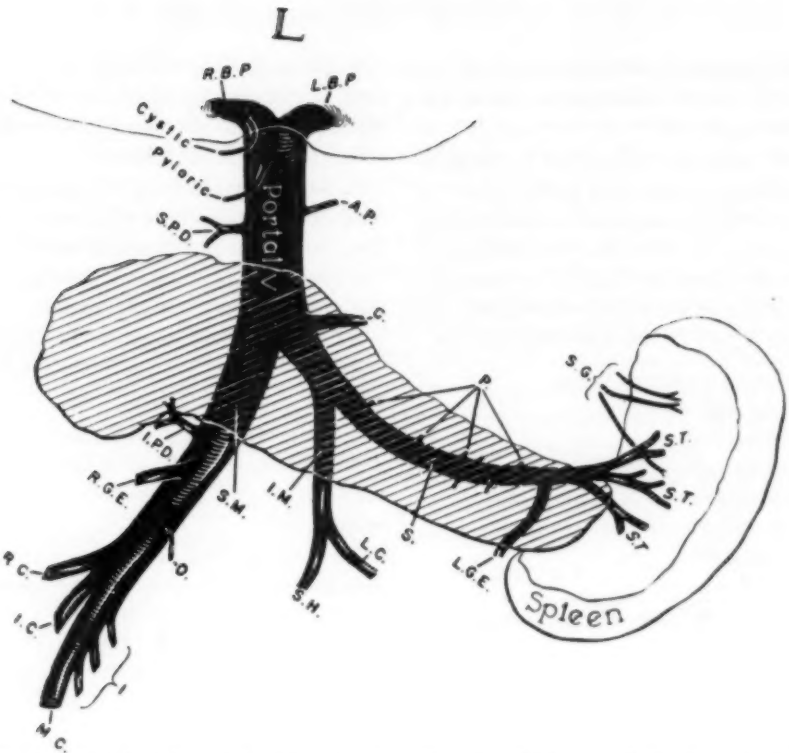

Fig. 1.—Extrahepatic portal system of veins. Reproduced with permission from Douglass, B. E.; Baggenstoss, A. H., and Hollinshead, W. H.: *Surg. Gynec. & Obst.* **91**:562 (Nov.) 1950.

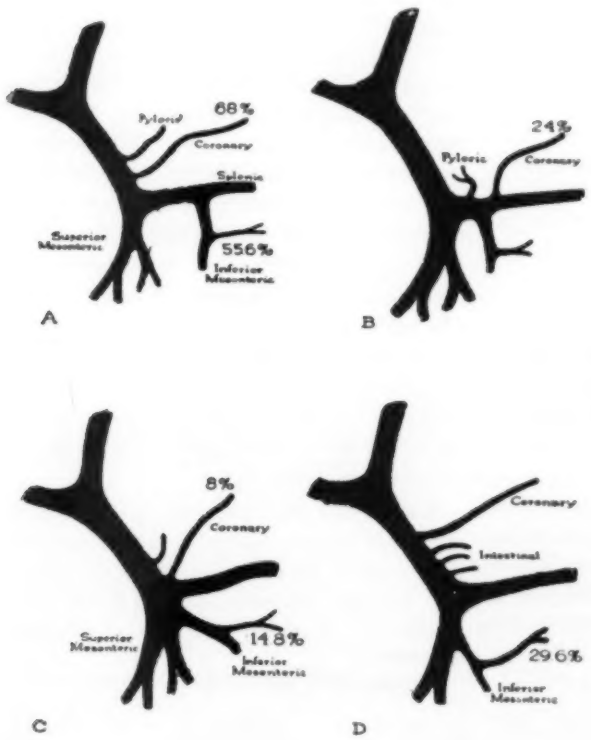

Fig 2.—Variations in morphology of the portal vein. Reproduced with permission from Gilfillan, R. S.: ARCH. SURG. **61**:449 (Sept.) 1950.

Rousselot [5] measured portal pressures during laparotomy was the existence of portal hypertension confirmed.

In 1945, Whipple [6] advocated a classification separating patients with portal hypertension into two major categories: those in whom the obstruction to portal flow is intrahepatic and those in whom the block is extrahepatic. A pathoanatomic variety of obstructive factors is presented in the following outline [7]:

I. Intrahepatic obstructive factors
- A. Congenital lesions
- B. Infiltrations
- C. Parenchymatous hepatitis
- D. Biliary lesions—cholestatic fibrosis
- E. Circulatory lesions—hepatic stasis
- F. Focal lesions
  - 1. Inflammatory
  - 2. Parasitic—schistosomiasis, clonorchiasis
- G. Neoplasms
  - 1. Primary
  - 2. Secondary
- H. Toxic—chloroform, etc.

II. Extrahepatic obstructive factors
- A. Congenital lesions
  - 1. Stenosis
  - 2. Angiomatosis
  - 3. Cruveilhier-Baumgarten syndrome
- B. Thrombosis
- C. Calcifications
- D. Compressions—pancreas, stomach, colon
  - 1. Inflammatory
  - 2. Tumors
    - (*a*) Benign (primary)
    - (*b*) Malignant (secondary)

Hepatic cirrhosis is the commonest cause of intrahepatic obstruction and can usually be diagnosed by routine clinical studies. Many theories have been proposed, but an explanation of the nature of the obstruction in intrahepatic disease remains unsolved.

Elevation in portal pressure should be considered the result of disease processes causing portal stasis rather than a single disease entity.[1] Regardless of etiology, portal hypertension may cause splenomegaly, hemorrhage from esophagogastric varices, and, if hepatic decompensation exists, ascites.

When portal hypertension due to intrahepatic or extrahepatic block is present, numerous extensive collateral venous channels develop, principally as follows:

1. At the two ends of the gastrointestinal tract where glandular and squamous epithelium unite. Esophagogastric varices form in the submucosa of the gastric cardia, and hemorrhoids form at the anus.

2. At the umbilicus where the portal bed and the anterior abdominal wall veins connect.

3. If the obstruction is extrahepatic numerous anastomotic channels develop in the immediate vicinity of the occluded portal or splenic vein.

Hemorrhage from esophagogastric varices manifested by hematemesis or progressive anemia and melena may be the first indication of portal disturbances. Roentgen examination of the esophagus may reveal varices, but this type of examination is not completely dependable. Direct visualization by esophagoscopy is preferable. Because the varices are vulnerable to mechanical trauma from swallowed food and diaphragmatic movements and mucosal ulcerations from regurgitated gastric juice, sudden massive exsanguinating hemorrhage may occur.* Contributing factors are coagulation defects, for example, thrombocytopenia resulting from hypersplenism and hypoprothrombinemia resulting from impaired liver function. The nonoperative treatment of cardioesophageal tamponade with a gastric balloon, as recommended by Sengstaken and Blakemore,[10] may suffice. Operative treatment includes injection of a sclerosing solution into varices, transesophageal suture of the varices, or gastric resection. However, unless surgical decompression of the portal bed is accomplished, the danger of hemorrhage always exists.

Abnormally high pressure in the splenic vein leads to hyperplastic splenic changes and may result in the reduction of one or more of the formed elements of the blood. The mechanism whereby the spleen produces

* References 8 and 9.

anemia, leucopenia, or thrombocytopenia is unknown, but the term hypersplenism has been applied to this condition. The size of the spleen varies widely and may be related to the availability of the compensatory collateral circulation, the latter depending on the site of portal obstruction.[7]

The formation of ascites in hepatic cirrhosis is a complex process representing so-called decompensation. The several factors involved in its formation are portal hypertension, altered salt and water metabolism, lowered plasma oncotic pressure due to hypoalbuminemia, excess antidiuretic hormone, and a vasodepressor mechanism.[11]

PORTAL VENOGRAPHY

Ancillary techniques for the preoperative diagnosis of portal hypertension have been devised recently. The ether rectum-to-lung circulation test and measurement of the pressure in the distended superficial abdominal veins have not proved dependable. The most promising is delineation of the portal venous system by injection of a radiopaque dye percutaneously or during laparotomy. Attempts to demonstrate the portal system by injection at operation of a radiopaque substance into the coronary vein or portal and splenic trunks were first performed by Blakemore and Lord,[12] in 1945.

Abeatici and Campi,[13] in 1951, first described a method of transperitoneal or percutaneous portal venography in a dog via the spleen and splenic vein, and Leger and co-workers [14] applied the same technique in man for the first time. Later in 1951 Boulvin and co-workers [15] described the technique of portal venography by transperitoneal route in great detail. Since that time a number of men have been responsible for continued investigation and improvements in visualization of parts of the portal system by roentgenographic techniques.

Valuable information may be obtained by means of splenic portography. Accurate preoperative knowledge of the status of the portal and splenic veins is important in view of the development of operations to accomplish portacaval or splenorenal shunting for decompression of the portal venous bed. The degree of portal hypertension and the obstructive site may be ascertained. The size and patency of the splenic and portal veins may indicate to the surgeon the identity and position of veins large enough for anastomosis. In splenomegaly of unknown etiology, splenic portography may reveal advanced pancreatic lesions or other retroperitoneal neoplasms impinging on the veins. The position of intrahepatic masses, such as neoplasms or abscesses, which alter the intrahepatic portal radicals may be visualized. If splenectomy is not performed at the time of portacaval anastomosis, the patency of the shunt may be demonstrated by splenic venography.

The following is a description of the usual technique of percutaneous splenic portography. The patient, previously determined to have splenomegaly and no hemorrhagic diathesis, is placed in a supine position on a radiographic table. After the splenic area is delineated by percussion, procaine is injected through the skin and underlying tissues in the 9th or 10th intercostal space in the midaxillary line. A 17-20 gauge spinal or thin, flexible needle is passed through the abdominal wall and peritoneum (at which point the patient feels slight discomfort) and directed medially and posteriorly until a soft, elastic scraping resistance of the splenic capsule is felt over the needle tip with each respiration. The patient is requested to inspire and hold his breath, at which time the needle is thrust 2-3 cm. obliquely into the spleen in the direction of the hilus so that a reflux of the dye subcapsularly and perisplenically is avoided. Ten to thirty cubic centimeters of a contrast medium, preferably 70% sodium acetrizoate (Urokon), is rapidly injected in three to four seconds. During the fourth second the first x-ray exposure is made and the needle withdrawn. Serial x-rays with roll film cassettes provide a graphic survey of changes in the opacification of the venous system and of the hemodynamic conditions in its venous segments.†

† References 7 and 16.

For the children on whom this procedure has been done at the Research and Educational Hospitals, University of Illinois, modification of the basic technique was necessary. To insure control of respirations, the procedure was performed on the operating table with the patient under general anesthesia immediately prior to laparotomy. The films were immediately developed so the findings could serve as a guide to the surgeon.

In a normal splenic venogram the splenic vein and the portal vein and its branches for some distance inside the liver are visible in about three seconds after injection of the contrast medium. The dye leaves the spleen very rapidly, the opacification rate being inversely proportional to the circulation rate, while the elimination rate is directly proportional to it.[17] In cases of extrahepatic venous block there is increased opacification proximal to the obstruction and decreased opacification distal to the obstruction. In hepatic cirrhosis, because the obstruction to the portal circulation is within the liver, the intrahepatic venous branches are either not visible or are faintly seen, depending on the degree of obstruction and portal hypertension.[18] The extrahepatic portal vein and the splenic vein appear markedly dilated and tortuous—hepatofugal flow is the term applied. The inferior mesenteric and coronary veins may not be demonstrated unless the portal hypertension is severe. Their prominence and tortuosity may be a measure of the degree of hypertension.

There have been less than 50 pediatric cases in whom the procedure has been performed thus far reported in the literature.‡ To date no undesirable complications of the procedure have been reported. There may be pain over the spleen for 5 to 10 minutes after the injection. Rarely the procedure is followed by vomiting. Overnight fasting and administration of morphine or chlorpromazine prior to the procedure will obviate these difficulties. Slight hemorrhage from the spleen may occur at the puncture site, but it stops spontaneously. Laceration of the splenic capsule and possible splenic rupture can occur unless the material is injected some distance inside the spleen. Additional precautions are as follows: the procedure should be limited to patients whose spleens are palpable; the sensitivity of the patient to the contrast material should be tested, and a small diameter needle should be used. The procedure should be avoided in presence of septic splenomegaly, hemorrhagic tendency, or lack of immediate facilities for emergency splenectomy. Detectable pathologic changes of importance have not appeared in the portal system or spleen as a consequence of the injection of the radiopaque material.[22]

TABLE 1.—*Extrahepatic Obstruction*

	Case 1, 3½-Yr. W. M.	Case 2, 7-Yr. W. F.
Varices or gastrointestinal bleeding	++ hematemesis	+++ hematemesis
Superficial abdominal venous distention	++	+
Spleen	1½ F*	2 F
Liver	1 F	1 F
Ascites	..	..
Liver-function tests	Normal	Normal

* F indicates fingerbreadths.

TABLE 2.—*Intrahepatic Obstruction*

	Case 3, 4½-Yr. W. M.	Case 4, 1-Yr. W. M.
Varices or gastrointestinal bleeding	+ gastrointestinal series	+ gastrointestinal series
Superficial abdominal venous distention	+++	+++
Spleen	4 F	2 F
Liver	3 F	2 F
Ascites	++	..
Liver-function tests	Abnormal	Abnormal

REPORT OF CASES

Following preliminary studies of splenoportal venography in dogs, the technique was applied to the study of portal obstruction in man. Resumés of illustrative cases observed at our hospital in the past year will be presented (Tables 1 and 2).

‡ References 19 to 24.

CASE 1.—The first case is that of a 3½-year-old white boy who had massive hematemesis and melena for one week prior to his hospital transfer. On admission he exhibited pallor, prominent superficial veins, moderate splenomegaly, and slight hepatomegaly. There was no ascites. Laboratory examination revealed anemia and leucopenia. Liver-function tests were normal. Fluoroscopy with barium revealed large esophageal varices. For this reason no esophagoscopy was done. Splenic portogram immediately prior to surgery revealed obstruction in the portal vein. A splenectomy and an end-to-side splenorenal shunt were performed. The operation was technically successful, but cardiac arrest occurred, and the patient died 14 hours after the surgery. Postmortem examination revealed two local strictures of the portal vein, with focal endophlebosclerosis. A greatly thickened gall bladder, bound by adhesions, was postulated to be the source of infection. The splenorenal anastomosis was patent at autopsy.

This case illustrates portal hypertension secondary to extrahepatic venous obstruction. These blocks, secondary either to a congenital malformation or thrombophlebitis involving the veins of the portal system, are not uncommon in children. The evidence at postmortem examination of previous gall bladder inflammation allows speculation that this may have been the source of portal vein infection.

The clinical picture of massive esophageal bleeding in the face of normal liver function is well demonstrated by this case. Without operative interference the prognosis is poor because the esophageal bleeding is recurrent and may lead to exsanguination. Previously splenectomy was the method of treatment, but it alone will not produce portal decompression. Moreover, by sacrificing the splenic vein, primary splenectomy deprives the surgeon of the opportunity of accomplishing a splenorenal shunt. While this patient died as a result of the operation, in our opinion the poor prognosis justified the surgical risk. It is unfortunate this accident occurred, for the anastomosis was technically satisfactory and a good result might have been anticipated.

CASE 2.—The second case, a 7-year-old white girl, had a five-month history of intermittent massive hematemesis and splenomegaly. On admission, pallor, moderate splenomegaly, slight hepatomegaly, and increased venous markings were found. Laboratory examination revealed a leucopenia and anemia. Liver-function tests were normal. Fluoroscopy with barium did not reveal esophageal varices. Large varices, however, were visualized by esophagoscopy.

Under general anesthesia immediately prior to operation, 10 ml. of sodium acetrizoate was injected through the abdominal wall into the spleen. The resulting portograms revealed an enlarged splenic vein with obstruction in the portal vein. At laparotomy splenic vein pressure manometrically measured 290 mm. of water, or two and one-half times normal value. After the splenic artery was ligated, a fall of only 10-15 mm. occurred, confirming the diagnosis of portal obstruction; for if the splenic vein alone were blocked, a drop in pressure to very nearly zero would have been noted. Splenectomy and a splenorenal shunt were performed. After the anastomosis, pressure in the vein fell and size of the vessel decreased.

Postoperatively the patient did well and has continued to be asymptomatic for the past year. Her blood cell counts have been normal, and esophagoscopy reveals only minimal esophageal varices with straining. Growth and development of the patient during the last year has been good. Although the presence of hematemesis from esophageal varices in a patient with normal liver function suggested the diagnosis, the presence of extrahepatic portal obstruction was established by percutaneous splenoportography. This type of thrombophlebitis may result from omphalitis in the neonatal period. However, pathogenesis of the portal thrombosis in this patient remains unknown.

CASE 3.—The third case is that of a 4½-year-old white boy who developed abdominal enlargement one week prior to hospitalization. Jaundice had been present from birth until its gradual subsidence at the age of 4 months. No hematemesis or melena had been noted, but frequent bruising and respiratory infections had occurred.

On admission marked superficial venous filling and abdominal enlargement were noted. Marked splenomegaly, hepatomegaly, and ascites were present. Laboratory examination revealed leucopenia and anemia. The liver-function tests were abnormal. Fluoroscopy with barium revealed esophageal varices.

After four months of medical preparation the patient was subjected to surgery. Splenic portography was attempted, but due to technical difficulties satisfactory films were not obtained. At operation cirrhosis of the liver was confirmed; a large, friable spleen was removed and a splenorenal shunt made.

This patient made a good recovery following surgery. Ascites was no longer present, and signs of hypersplenism disappeared. Six months postoperatively fluoroscopy with barium and esophagoscopy revealed no varices and there was slight improvement in liver-function studies.

This case illustrates portal hypertension secondary to intrahepatic obstruction. From the history we may surmise that this child suffered from neonatal infectious hepatitis. Formerly, jaundiced infants with neonatal hepatitis often died as a re-

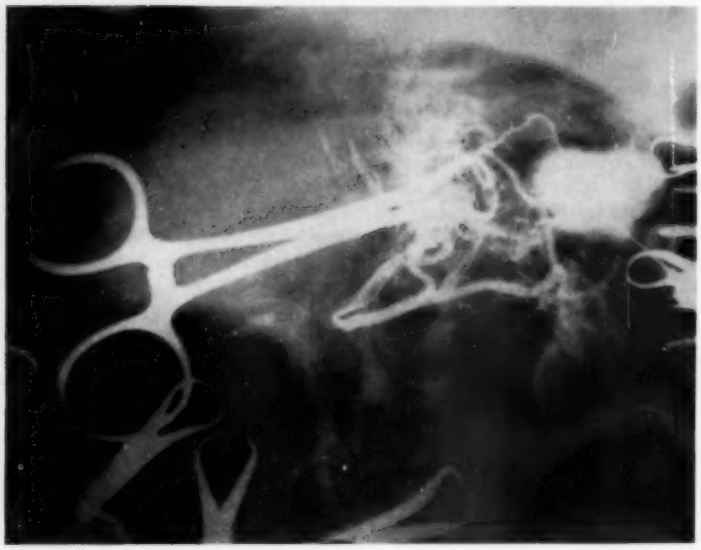

Fig. 3. — Splenoportogram in patient with cirrhosis.

sult of extensive operative procedures. With the more conservative management followed at present, it may be anticipated that more patients will live to develop portal hypertension secondary to cirrhosis. If the complications of portal hypertension can be avoided, with growth and good medical management sufficient liver regeneration may take place to maintain these patients in good health. Although patients with intrahepatic obstruction are a greater surgical risk because of their liver disease, the poor prognosis of unrelieved portal hypertension justifies surgical intervention in our opinion after medical preparation.

Case 4.—The last case was seen at the age of 1 year. Past history stated excessive bleeding following circumcision at 3 days of age. Jaundice, hepatomegaly, and abnormal liver function were present at 6 weeks, and splenomegaly at 3 months. The jaundice gradually subsided, but hepatomegaly and increasing splenomegaly continued to be found. Prepartal contact with known hepatitis was admitted by the mother.

On admission the child exhibited pallor, venous distention, and abdominal enlargement. Marked splenomegaly, hepatomegaly, and a small hemorrhoid were found, but no ascites. Laboratory examination revealed anemia, moderate aberration of liver function, and absence of Rh or ABO incompatibility. Fluoroscopy with barium revealed no varices.

After a period of preparation for optimum operative conditions, a splenic portogram was obtained at laparotomy. Percutaneous injections of the spleen were unsuccessful. The splenoportogram shown in Figure 3 was obtained after the abdominal wall was opened. A patent splenic and portal vein

Table 3.—*Summary of Cases*

	"Hypersplenism"		Esophageal Varices	
	Preop.	Postop.	Preoperative	Postoperative
Extrahepatic				
Case 1	+	0	Hematemesis ++ Barium swallow +	0
Case 2	++	—	Hematemesis +++ Barium swallow — Esophagoscopy ++	Hematemesis — Barium swallow — Esophagoscopy — to +
Intrahepatic				
Case 3	++	—	Hematemesis — Barium swallow +	Hematemesis — Barium swallow — Esophagoscopy —
Case 4	+	..	Hematemesis — Barium swallow — Esophagoscopy +	.....

with little medium in the liver and a remarkable number of hepatofugally filled collateral veins are demonstrated. No extrahepatic obstruction is seen. Splenectomy and splenorenal shunt were made. The immediate postoperative recovery has been good.

From the history we may surmise this infant suffers from cirrhosis secondary probably to intrauterine hepatitis, since there was no evidence of blood incompatibility with the mother. The operation in this case may be considered palliative, since advanced cirrhosis was revealed by the operation.

Table 3 demonstrates that preoperatively depression of formed blood elements, splenomegaly, and esophageal varices were present in all cases. Hematemesis was the complaint in both cases of portal-vein obstruction. Although no bleeding had as yet occurred in the patients with cirrhosis, varices were demonstrated.

Postoperatively the second and third patients have normal blood values and growth increments and minimal to no evidence of varices. Conclusions on the last patient must be deferred until sufficient time has passed.

In all of these cases splenectomy and splenorenal anastomosis were performed. Should the splenorenal shunt fail to remain patent or prove inadequate with growth of the child, a portacaval shunt can still be established in the patients with intrahepatic obstruction. We believe the prognosis in the three surviving children has been greatly improved.

SUMMARY

Early recognition and accurate diagnosis of portal hypertension in children is important to prevent medically and surgically the complications of serious hemorrhage and "hypersplenism."

A review of the portal venous system anatomy and obstructive factors is given.

By means of portal venography the site of portal obstruction may be demonstrated.

The indications, technique, and precautions of percutaneous transplenic venography are presented. Although the procedure has been safe in the reported cases, possible complications are discussed.

Four illustrative cases of portal hypertension treated in the past year on whom splenic portography was attempted are presented.

REFERENCES

1. Child, C. G., III: The Hepatic Circulation and Portal Hypertension, Philadelphia, W. B. Saunders Company, 1954.

2. Douglass, B. E.; Baggenstoss, A. H., and Hollinshead, W. H.: The Anatomy of the Portal Vein and Its Tributaries, Surg. Gynec. & Obst. **91**:562 (Nov.) 1950.

3. Gilfillan, R. S.: Anatomic Study of the Portal Vein and Its Main Branches, Arch. Surg. **61**:449 (Sept.) 1950.

4. Gilbert, A., and Weil, É.: Sur la Tension des liquides ascitiques, Soc. Biol. **1**:511 (June) 1899.

5. Rousselot, L. M.: The Late Phase of Congestive Splenomegaly (Banti's Syndrome) With Hematemesis but Without Cirrhosis of the Liver: Further Observations on Etiology of Banti's Syndrome and Effect on Prognosis of Certain Variations in Portal Venous Pattern, Surgery **8**:34 (July) 1940.

6. Whipple, A. O.: The Problem of Portal Hypertension in Relation to the Hepatosplenopathies (E. Starr Judd Lecture), Ann. Surg. **122**:449 (Oct.) 1945.

7. Dogliotti, A. M., and Abeatici, S.: Transparietal Splenoportal Roentgenography and Research on Portal Hypertension, Surgery **35**:503 (April) 1954.

8. Tocantins, L. M.: Hemorrhagic Tendency in Congestive Splenomegaly (Banti's Syndrome), Its Mechanisms and Management, J. A. M. A. **136**:616 (Feb. 28) 1948.

9. DeCamp, P. T.: The Surgical Treatment of Portal Hypertension, S. Clin. North America p. 975 (Aug.) 1953.

10. Sengstaken, R. W., and Blakemore, A. H.: Balloon Tamponage for the Control of Hemorrhage from Esophageal Varices, Ann. Surg. **131**:781 (May) 1950.

11. Habif, D. V.; Randall, H. T., and Soroff, H. S.: The Management of Cirrhosis of the Liver and Ascites with Particular Reference to the Portacaval Shunt Operation, Surgery **34**:580 (Sept.) 1953.

12. Blakemore, A. H., and Lord, J. W., Jr.: The Technic of Using Vitallium Tubes in Establishing Porta-Caval Shunts for Portal Hypertension, Ann. Surg. **122**:476 (Oct.) 1945.

13. Abeatici, S., and Campi, L.: Sur les Possibilités de l'angiographie hépatique—la Visualisation du système portal recherches expérimentales, Acta radiol. **36**:383 (Nov.) 1951.

14. Leger, L.; Gally, L.; Arvay, N.; Oudot, J., and Auvert, J.: La Portographie (technique et indications), J. radiol. et électrol. **32**:633, 1951.

15. Boulvin, R.; Chevalier, M.; Gallus, P., and Nagel, M.: La portographie par voie splénique transpariétale, Acta chir. belg. **50**:534 (Nov.) 1951.

16. Tori, G., and Scott, W. G.: Improved Method for Splenoportography Using Biplane Serialized Exposures, Am. J. Roentgenol. **70**:237 (Aug.) 1953.

17. Abeatici, S.; Campi, L., and Ferrero, R.: Sulle curve di propagazione del circolo splenoportale: Studio emodinamico del distretto lieno-epatico mediante portografia seriata, Minerva chir. **7**:886 (Dec. 15) 1952.

18. Konar, N. R. and Sen Gupta, A. N.: Splenic Venography. Brit. M. J. **2**:810 (Oct.) 1953.

19. Bahnson, H. T.; Sloan, R. D., and Blalock, A.: Splenic-Portal Venography: Technique Utilizing Percutaneous Injection of Radiopaque Material into Spleen, Bull. Johns Hopkins Hosp. **92**:331 (April) 1953.

20. Gvozdanovic, V.; Hauptmann, E.; Najman, E., and Oberhofer, B.: Percutaneous Splenic Venography, Acta radiol. **40**:17 (July) 1953.

21. Sansone, G.: Lo Studio radiologico dei vasi portali, Minerva pediat. **5**:680 (Aug.) 1953.

22. Hallenbeck, G. A., and Bruwer, A.: Portal Venography, Proc. Staff Meet. Mayo Clin. **29**:333 (June 16) 1954.

23. Hollenberg, H. G., and Briggs, B. P.: Portal Caval Anastomosis in Infants, Ann. Surg. **141**:648 (May) 1955.

24. El-Gholmy, A.; Grace, H.; Ragab, M.; Nabawy, M.; Gabr, M., and Hashim, N.: Splenoportal Venography in Infancy and Childhood, J. Pediat. **46**:506 (May) 1955.

News and Comment

ANNOUNCEMENTS

United Cerebral Palsy Research and Educational Foundation.—In order to accelerate the research attack on the complex problem of cerebral palsy, a special Research and Educational Foundation has been established by United Cerebral Palsy and a group of interested industrialists, as announced by Jack Hausman, UCP President.

At an organization meeting of the new foundation held on Sept. 30, the following officers were elected: Chairman of the Board, Leonard H. Goldenson, of New York, President of American Broadcasting-Paramount Theatres, and also Chairman of the Board of United Cerebral Palsy; President, Jack Hausman, of New York, President of M. Hausman & Sons, and also President of UCP; Vice-President, Roger S. Firestone, of Pottstown, Pa., President of Firestone Plastics Co.; Vice-President, William Clay Ford, of Detroit, Vice President, Ford Motor Company; Vice-President, Joseph A. Martino, of New York, President of National Lead Co.; Treasurer, William C. Langley, of New York, Partner, William C. Langley Co.; Asst. Treasurer, Howard R. Mears Jr., of Fanwood, N. J., Second Vice-President, Chase-Manhattan Bank.

Mr. Hausman explained that the United Cerebral Palsy Research and Educational Foundation, Inc., will seek to develop additional support for research into cerebral palsy and for additional grants for the training of specialists in this field. It will seek gifts from industry, corporations, and foundations. These gifts will be added to the funds set aside for research and training by United Cerebral Palsy and its nationwide network of affiliates, each of which allocates a percentage of contributions for the national program.

Case Reports

TREATMENT OF TETANUS OF THE NEWBORN

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TETANUS of the newborn, formerly nearly always fatal, has been more amenable to therapy in recent years; antiserum, sedation, and penicillin have improved the prognosis.* The nutrition of these patients has continued to present a problem to pediatricians; at the meeting of the American Pediatric Society in 1954 the problem was referred to as very difficult.[8] It is therefore the purpose of the present report to point out the advantages of the percutaneous intravenous drip when combined with the "room within a room" protective effect of an incubator. Most of the baby's needs may be satisfied without repeated pain, handling, noise, flashing lights, or other undesirable stimuli. A decrease in number and intensity of such stimuli is followed by a decreased incidence of those events which are most likely to end the case fatally: tetanic convulsive or laryngospastic episodes. It also follows that the amount of sedation may be reduced and oversedation avoided.

In 1944 we reported, as part of a study on parenteral administration of amino acids to infants and children, successful maintenance of a child with tetanus by percutaneous intravenous drip.[9] At that time, and since, percutaneous intravenous feeding has been used in all types of patients, to the exclusion of the "cut-down" method. The needles were fixed in veins with collodion-soaked cotton. More recently the method has been made very secure by fixation of the barrel of the needle alone (Gardiner-Murphy modification).[10] The following case is presented as an illustration of the fact that the method is easily utilized in the care of the newborn with tetanus.

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* References 1-7.

REPORT OF A CASE

The patient was delivered uneventfully in the hospital at Red Lodge, Mont., by Dr. Milton Coutu, May 26, 1954. Successfully breast fed, he was discharged home to the family ranch, where horses are part of the daily life, on the fourth day. His mother changed the gauze covering on the cord at home that day. On the 6th day, a very foul odor caused her to change the gauze daily until the rotting stump fell off, on the 10th day. No local medication was used by her at any time.

On the 10th day of his life his mother experienced difficulty in getting him to nurse; she resorted to prying his mouth open. When this failed, she attempted bottle feedings without success. She observed that any stimulation (diaper-changing, attempted feeding, and the like) resulted in a convulsive seizure in which he stiffened into an arched position, fists clenched against his chest, and breathed with difficulty. He was therefore readmitted to the Red Lodge hospital the following day; oral feedings proved impossible, and so subcutaneous fluids were given. Tetanus antitoxin, 1500 units, was given.

The 13th day of life, he was transferred to St. Vincent Hospital, Billings, Mont. On arrival his temperature was 104.8 F. He was in a continuous tetanic convulsion, with cyanosis, stertorous respiration, and a tightly closed mouth. As emergency therapy he was given oxygen by mask, a cold wet sheeting, and ¼ grain (15 mg.) of phenobarbital sodium intravenously; the generalized seizure stopped, respirations became regular, and cyanosis disappeared, though he remained stiff and his mouth remained closed. Blood and spinal fluid were then obtained, with these results: serum calcium, 10 mg/100 cc.; glucose, 81 mg/100 cc.; nonprotein nitrogen, 39.5 mg/100 cc.; the clear spinal fluid contained 6 lymphocytes/cu. mm.; protein, 57 mg/100 cc.; glucose, 74 mg/100 cc. The clean, dry umbilicus was cultured, but no clostridia were recovered.

Tetanus antiserum, 31,500 units, was given intramuscularly. An intravenous drip was started with a No. 22 needle, sealed in a scalp vein with col-

lodion-soaked cotton. Replaced only once, this served for food and medication for the next 12 days. He was kept nude in an incubator in a darkened room. Oxygen was started at 6 liters a minute. Basal sedation was with phenobarbital sodium, ¼ grain every six hours for five days and every eight hours thereafter. When a severe convulsive seizure occurred despite this, 1 cc. of paraldehyde with oil was given by rectal tube; this was done six times in the first three days but was unnecessary thereafter. A total of 300,000 units of penicillin was given daily.

The parenteral feedings were accomplished by continuous drip at four to six drops per minute. Dextrose, 10%, containing added vitamin B complex and ascorbic acid (1 cc. of Solu-B with C per 500 cc. of 10% dextrose), was alternated with 6% amino acids and 5% dextrose containing 2 mEq. of KCl per 100 cc. (Hyprotigen). In all, 4500 cc. was given over a period of 12 days, providing about 26 Cal. per pound per day. The baby's initial weight was 8 lb. 1 oz.; at the end of the 12 days it was 7 lb. 13 oz. We were well pleased at this slight loss.

After the first three days his course was uneventful. Oxygen was then reduced to 2 liters a minute for several days, then discontinued. Disturbances incident to removal of diapers that were simply laid in place provided the only stimuli; resultant seizures were brief. After the 12th day even these brief seizures ceased, though the patient remained very stiff for weeks. A plastic tube was then used for feedings for five days; when he began to nurse the tube, bottle feedings were started. On discharge, his mother was instructed to provide a form of passive physical therapy during and after a warm bath twice daily. Seen almost a year later, he is apparently a normal baby.

COMMENT

The prognosis in neonatal tetanus is reputedly poor when there is high fever and when incubation period is short. Our patient had a temperature of 104.8 F on admission, and the incubation period was probably six days. Recovery occurred despite these. It seems logical to suggest that this result is related to the diminution of stimulation made possible by the percutaneous intravenous drip and the isolation of the nude baby in the incubator. The protective "room within a room" effect, with administration of food and medicine by quiet changing of flasks and injections into tubing outside the patient's room seems such a constructive way to handle these most sensitive patient that I should like to recommend that it be tried in all size groups. For the large patient, soft, sound-absorbing drapes, transparent in part, may well be used to provide the same effect. A low and constant level of illumination may be provided in some indirect manner (such as a small light under the bed).

The nutritional goal was simple maintenance, in our baby's case. It is theoretically feasible to provide more calories with fat emulsions and more concentrated glucose-amino acids solutions, but this is questionably necessary.

SUMMARY

The treatment of tetanus of the newborn may be facilitated by the protection from stimulation made possible by the combination of the "room within a room" effect of an incubator in a dark quiet room and the administration of food and medications by slow percutaneous intravenous drip. It is suggested that this combination be tried in all sizes of tetanus patients. An illustrative case is presented.

REFERENCES

1. Block, W. M., and Foster, M. J.: Tetanus of the Newborn Infant, J. Pediat. **34**:633, 1949.

2. Dietrich, H. F.: Tetanus Neonatorum, J. A. M. A. **147**:1038, 1951.

3. Edmonds, A. R., and Lavers, K. W.: Treatment of Tetanus, with Report of a Case of Tetanus Neonatorum in Which Recovery Occurred, M. J. Australia **2**:564, 1949.

4. Friedlander, F. C.: Tetanus Neonatorum: Report on 8 Cases with 2 Recoveries, J. Pediat. **39**:448, 1951.

5. Kao, Y. E.: Tetanus Neonatorum, Chinese M. J. **69**:512, 1951.

6. Negro, R. C., and Tolosa, M.: Tetanus of the Newborn, Arch. pediat. Uruguay **17**:289, 1946.

7. Monsky, D. B.: Tetanus Neonatorum, South. M. J. **33**:67, 1940.

8. Forbes, G. B., and Auld, M.: Management of Tetanus: Report of 15 Cases with Recovery, A. M. A. Am. J. Dis. Child. **88**:385, 1954; discussion, p. 387.

9. Hartmann, A. F.; Lawler, H. J., and Meeker, C. S.: Studies of Amino Acid Administration, J. Pediat. **24**:371, 1944.

10. Abella, P. U.: The Use of the Gardiner-Murphy Pediatric Scalp Vein Outfit, J. Pediat. **43**:709, 1953.

TREATMENT OF STILL'S DISEASE WITH ISONIAZID

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UNDER the title, "Rimifon and Still's Disease," we previously published a preliminary report on a case of Still's disease, or atrophic rheumatoid arthritis. Furthermore, under the title "Isonicotinic Acid Derivatives in Different Abnormal Conditions," we have reported to the Greek Pediatric Society on Feb. 24, 1953, a summary of the therapeutic effects of isoniazid in the same case to the above date.

REPORT OF A CASE

M. K., a girl aged 6 years, was admitted to the hospital on July 13, 1952. She was the second child of healthy parents and was born without complications after a normal pregnancy. One year prior to admission she underwent a tonsillectomy. At the time of admission she had a nine-month history of moderate fever and painful, gradually swelling joints, fusiform in shape, with stiffness and limitation and loss of movement. She was cachectic and melancholy.

Physical examination on admission revealed pallor, sunken eyes, cachexia, rachitic rosary, wing-like appearance of the shoulder blades, underdevelopment of the lower jaw, hypertrichosis of the arms and lower extremities, short fingers, and fusiform swelling of the knees, wrists, elbows, fingers, and ankles. There was severe muscular atrophy as well as superficial lymph node enlargement and minimal enlargement of the spleen. The neck exhibited pain and stiffness as well as limitation of movement, and there was severe limitation of motion in the joints. Every moment provoked intense pain, causing the patient to cry or weep. She remained bedridden, motionless, sad, and indifferent to her surroundings and was unable to care for even her more elementary needs.

Laboratory results were as follows: Tuberculin skin tests (Pirquet and Mantoux 1:10,000) negative; Wassermann reactions of the blood and cerebrospinal fluid and Widal and Wright reactions negative; blood and urine cultures sterile; sputum cultures for the tubercle bacillus and cocci negative; examination of the peripheral blood showed RBC 3,200,000 per cubic millimeter; hemoglobin 58%; WBC 8900 per cubic millimeter, with 47% polymorphonuclears, 51% lymphocytes, 2% monocytes. The sedimentation rate was elevated from 62 mm. after the first hour to 117 mm. after the second. Urinalyses were normal. Roentgenograms of the chest were also normal. X-rays of the joints revealed narrowing of the joint spaces with considerable atrophy of the bones. E. N. T. examination was normal. Serum levels of calcium and phosphorus were normal, and the alkaline phosphatase was 8 King-Armstrong units per 100 ml. The patient's weight was only 12.5 kg., that of a child of 2 or 3 years of age.

The patient was given isoniazid, 5 mg. per kilogram of body weight, each day for five months, and after discontinuance for thirty-eight days the same dosage was administered each day for an additional four months.

Results of the first period of treatment showed in the first month a reestablishment of appetite, a 600 gm. weight gain, diminution of pain on motion of the limbs, and increased interest of the patient in her surroundings. The fever continued to be septic in type, the temperature sometimes reaching a high of more than 100.4 F, seldom to 103.1 F. The sedimentation rate remained elevated (58 and 105 mm.). During the second month, recovery was more marked. Body weight increased by 1000 gm., and pain in the joints was considerably more reduced as well as the swelling. The patient began to stay awake longer, and to sit up, stand, and walk. The fever continued to be septic (temperature to 102.6 F). The sedimentation rate stayed elevated (78 and 130 mm.).

During the third month there was no pain. The patient walked more easily and performed her everyday needs by herself. She began talking to other children. The joint deformity became less marked than before. The body weight increased by 400 gm. The fever became intermittent, and the sedimentation rate continued to be elevated (80 and 120 mm.).

Recovery was even greater during the fourth and fifth months. The patient spoke, walked, and played as normally as any child. She complained of no pain. Movements of the head and limbs were executed easily. Deformity of the joints was dimin-

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ished and minimal. A gain of weight of 500 gm. for the two months was accomplished. The temperature became normal, but the sedimentation rate was high at 90 and 125 mm.

After discontinuance of treatment for a 38-day period, isoniazid was again administered at the same dosage per day. The sixth month of treatment showed a gain of weight of 900 gm., the seventh and eighth months a 500 gm. gain, and the ninth month 1100 gm. The patient was afebrile. She was affable and was normally active in play. Active and passive movements of all joints were executed easily and completely. Deformities of the joints became even less noticeable. While walking, the patient exhibited slight lordosis. Hypertrichosis was light. The sedimentation rate gradually fell from 72 and 118 mm. the sixth month, 55 and 70 mm. during the seventh and eighth months, to normal during the ninth month. General examination of the peripheral blood gave normal values. X-ray examination demonstrated restoration of the affected joints to normal, with some osteoporosis present from the patient's being bedridden for several months.

SUMMARY

A case of Still's disease is described, presenting an advanced state of cachexia, with complete impairment of limb function, extreme muscular weakness, intense pain, and melancholy.

A treatment of nine months' duration with isoniazid in daily doses of 5 mg. per kilogram of body weight caused no sign of toxicity.

Recovery of active and passive motion of the limbs was accomplished under the above period of treatment.

Pain ceased and the temperature dropped to normal.

There was marked improvement in nutrition.

The patient presented a picture of physical and mental well-being.

Restoration of the blood picture and x-rays of the joints to normal was observed.

CONCLUSION

Administration of isoniazid in the dosage of 5 mg. per kilogram of body weight in a case of severe Still's disease resulted in complete remission of all signs and symptoms of that disease during a nine-month period of treatment with the drug.

News and Comment

ANNOUNCEMENTS

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Progress in Pediatrics

CARCINOMA OF THE THYROID GLAND IN CHILDREN

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CARCINOMA of the thyroid gland in children has been the subject of numerous publications. Pemberton and Black [1] noted that 18 children, including 12 previously reported by Kennedy,[2] had been treated for carcinoma of the thyroid at the Mayo Clinic before 1944. In 1953 Winship and Chase [3] collected from the literature 230 cases of carcinoma of the thyroid among children, including the cases described by Pemberton and Black.

The present report comprises a review of our total experience wtih carcinoma of the thyroid in children up to 15 years of age seen at the Mayo Clinic through 1954. In reviewing the material for this study all pathologic specimens were reexamined, and in a few instances the pathologic type or grade of carcinoma has been changed. One case originally considered carcinoma was reclassified as reticulum-cell sarcoma that probably was not primary in the thyroid and was excluded from the series. In every patient included in this report the diagnosis of carcinoma was confirmed by careful examination of adequate pathologic specimens.

A total of 41 patients, 10 boys and 31 girls, are included in the study. The ratio of approximately three girls to one boy (75%) corresponds roughly to the ratio of 66% girls reported for the United States.[4] Figure 1 represents the distribution of patients according to year of diagnosis. It suggests that carcinoma of the thyroid has been recognized with increasing frequency during the past few years.

The distribution of patients according to age at the time of diagnosis is presented in Figure 2. In two patients the diagnosis was established during the fifth year of life. There were patients in each of the succeeding one-year age groups, the peak occurring at age 13. No effort was made to locate those pa-

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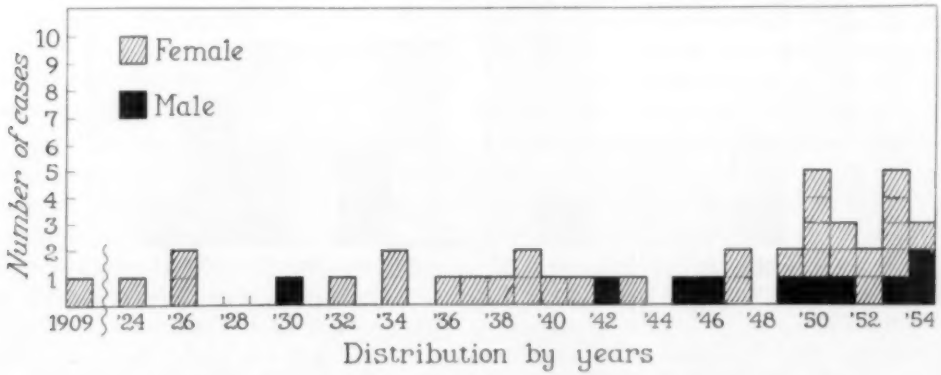


Fig. 1.—Distribution of patients according to year of diagnosis of thyroid carcinoma.

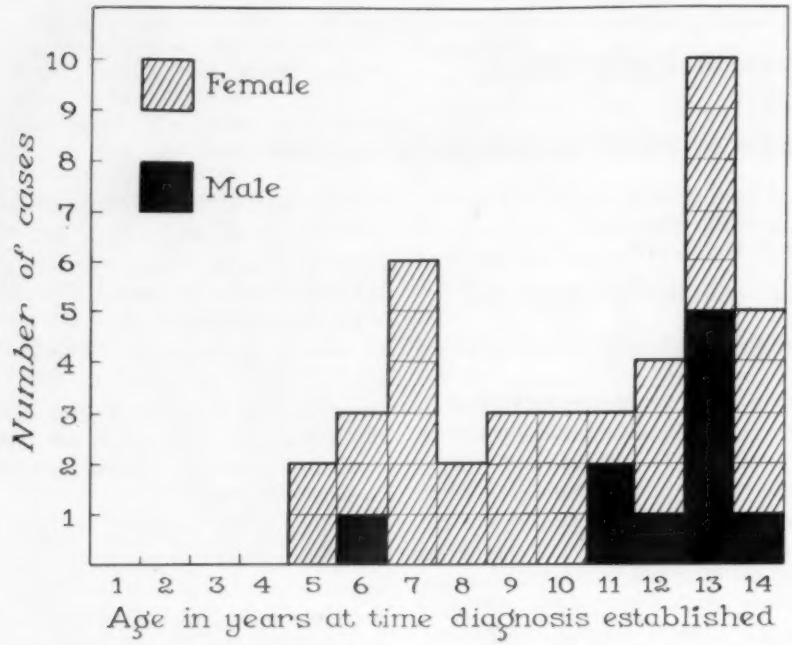


Fig. 2.—Distribution of patients according to age at time of diagnosis of thyroid carcinoma.

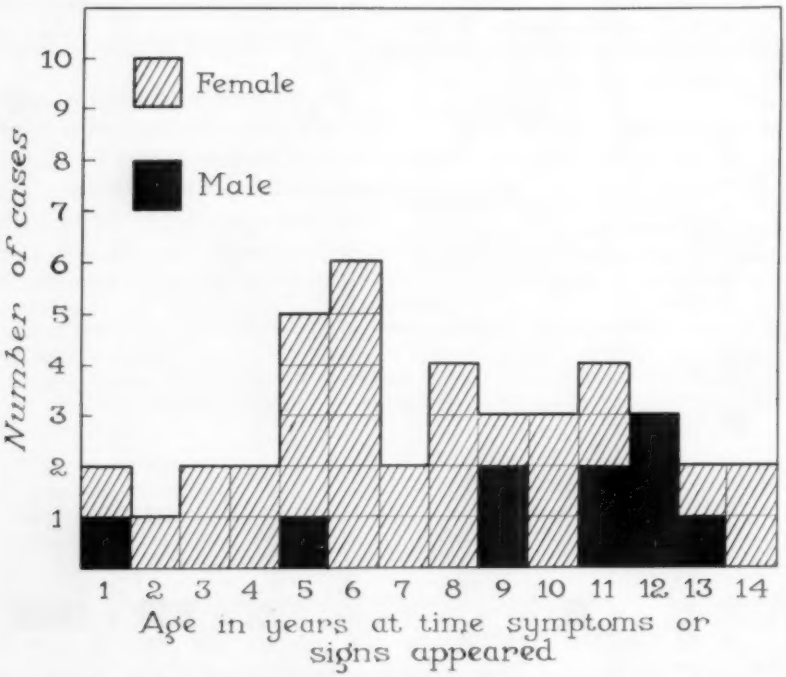


Fig. 3.—Distribution of patients according to age at the time the symptoms or signs of thyroid carcinoma were first recognized.

tients who had had symptoms of thyroid carcinoma before their 15th birthday but who had not sought medical care until after the age of 15.

Figure 3 gives the distribution of patients according to age at the time symptoms or signs were first recognized. Seven patients had evidence of disease before they were 5 years old, and two had enlarged lymph nodes which had been palpated during infancy. The average duration of the disease before the diagnosis was established was slightly more than two and one-half years. The longest period of observation before the diagnosis was established was 13 years, while the shortest was approximately 3 weeks. In 27 of the 41 patients symptoms or signs had been present for two years or less.

The diagnosis of cancer of the thyroid can be established only by histologic examination, but the disease presents a clinical picture which is so characteristic as to be strongly suggestive of its presence. Thyroglossal-duct cyst, branchial-cleft cyst, benign adenoma of the thyroid, colloid goiter, tuberculous adenitis, chronic lymphadenitis, and lymphoma were diagnoses mentioned by various observers of the patients in this series. According to the history, all the patients had had a palpable mass in the neck which had not been associated with preceding infection or systemic reaction. Two patients complained also of respiratory obstruction, and a third complained of hoarseness. Thirty-three patients had palpable cervical lymph nodes as a result of thyroid carcinoma at the time of admission to the Mayo Clinic; in thirty-one the enlarged nodes were confined to one side of the neck, and in two they were palpable on both sides of the neck.

Nine of the forty-one patients had metastatic involvement of the lymph nodes of both sides of the neck at some time during the course of the disease. Eight patients had palpable lesions of the thyroid alone, but one of these was found to have involvement of lymph nodes by cancer at the time of operation. Thus, all except seven patients were proved to have metastasis to the cervical lymph nodes. The number of lymph nodes involved varied, but in most cases not more than three or four were palpable on the original examination. Lymph nodes affected by thyroid carcinoma have a rather characteristic feel. They are firm, usually movable, nontender, and discrete and in most cases are members of the tracheoesophageal or jugular chain of lymph nodes in the neck. A majority of the nodes varied between 1 and 2 cm. in diameter. In our experience, fixation or matting of the cervical lymph nodes by thyroid carcinoma is seen only late in the course of the disease.

The thyroid gland should be carefully palpated in every child who has enlarged nontender cervical lymph nodes. If enlargement of these nodes is the result of metastasis from thyroid carcinoma, the thyroid gland will almost always be found abnormal on palpation. In some cases the gland has been described as diffusely enlarged, slightly enlarged, or firmer than normal, but in most cases a firm, nontender nodule has been palpated. In the present series, 38 patients were considered to have abnormality of the thyroid gland on palpation at the time of the original examination, and only 3 patients had small primary lesions of the thyroid that were not palpable before operation. In an occasional patient the primary tumor was large enough to produce respiratory symptoms by displacing the trachea. Nine of the thirty-eight patients were considered to have abnormalities involving both lobes of the thyroid on clinical examination. We should like to emphasize that the presence of enlarged, firm, discrete lymph nodes in the cervical region, when associated with palpable abnormality of the thyroid gland, is strong evidence of thyroid carcinoma. Every patient presenting this picture should be subjected to surgical exploration so that the correct diagnosis can be established and proper treatment instituted. Laboratory studies have been of little help in establishing the diagnosis of carcinoma of the thyroid although they sometimes aid in excluding other conditions.

TABLE 1.—*Carcinoma of the Thyroid Gland in Children: Classification of Cases* *

Case	Sex	Age, Yr.	Yr. Seen	Duration, Yr.	Pathologic Diagnosis	Nonsurgical Treatment	Follow-up, Yr.	Comment
Group A. Carcinoma of Thyroid Without Metastasis Treated by Surgical Excision Followed by External Irradiation								
1	F	7	1926	1	Encap. solid and follic. ca. (malig. adenoma)	Radium	24	Living and well 1950; untraced since 1950
2	M	14	1930	2	Solid ca., Gr. 2	Radium	20	Died 1950; pulmonary metastasis 1950
3	F	7	1934	2¼	Encap. solid and follic. ca., Gr. 1 (malig. adenoma)	Radium	15	Living and well 1949; keloid
4	F	13	1937	3	Follic. ca.	X-ray	17	Living and well 1954
5	F	13	1938	13	Follic. ca.	Radium	2	Untraced since 1940
6	F	7	1943	1	Follic. ca.	Radium	7	Living and well 1950; untraced since then; cong. absence, rt. lobe of thyroid; myxedema
7	M	13	1949	½	Follic. and solid ca., Gr. 1 (malig. adenoma)	Radium	5	Living and well 1954; benign adenoma of thyroid removed 1953
Group B. Carcinoma of Thyroid with Cervical Lymph-Node Metastasis Treated by Subtotal Thyroidectomy and Excision of Nodes								
8	F	12	1909	10	Papil. ca.	Radium	18	Subtotal resection of thyroid 1909 (E), 1913, and 1917; died 1927 (cause?)
9	F	7	1938	2	Mixed papil. and follic. ca.	X-ray	1	Subtotal thyroidectomy elsewhere 1938; chest metastasis 1939; died 1939
10	F	12	1939	¾	Follic. ca.	Radium	15	Living and well 1954
11	F	10	1941	2	Mixed papil. and follic. ca.	Radium	13	Metastatic cervical nodes removed 1951 and 1952 (E); living and well 1954
12	M	13	1945	2	Mixed papil. and follic. ca.	X-ray 1945 and 1949	9	Metastatic cervical nodes removed 1949 (E); living and well 1954
13	M	13	1946	4	Follic. ca.	Radium	7	Metastatic cervical nodes removed 1947; no evidence of recurrence 1953; patient mentally ill
14	F	9	1949	3	Mixed papil. and follic. ca.	X-ray (E)	4	Living and well 1953
15	M	13	1950	⅝	Papil. ca.	Radium	4	Living and well 1954
16	F	14	1950	¼	Papil. ca.	Radium	4	Subtotal thyroidectomy 1950 (E); metastatic nodes 1950; living and well 1954
17	F	7	1950	4	Mixed papil. and follic. ca.	I^{131}	4	Myxedema; tracheotomy; living and well 1954 but had palpable cervical nodes
18	F	6	1950	1	Mixed papil. and follic. ca.	Radium	4	Living and well 1954
19	F	7	1950	1	Mixed papil. and follic. ca.	None	4	Living and well 1954
20	F	8	1951	2½	Follic. ca.	None	3	Tracheotomy 1950; metastatic cervical nodes removed 1954; living and well 1954
21	F	13	1951	½	Papil. ca.	Radium	3	Cervical lymph node with metastases removed 1952; living and well 1954
22	M	10	1951	10	Mixed papil. and follic. ca.	None	3	Operation in 2 stages; living 1954, with chest metastasis
23	F	11	1952	1/12	Mixed papil. and follic. ca.	None	2	Cervical nodes with metastases removed 1954; living and well 1954
24	F	14	1953	⅛	Mixed papil. and follic. ca.	None	1	Cervical nodes with metastases removed 1954; living and well 1954
25	F	14	1953	½	Mixed papil. and follic. ca.	None	1	Tracheotomy due to small amount of postoperative bleeding; living and well 1954
26	M	13	1953	2	Mixed papil. and follic. ca.	None	1	Living and well 1954
27	F	6	1953	¼	Mixed papil. and follic. ca.	None	..	Adenoma of thyroid and cervical node with thyroid carcinoma removed elsewhere 1953; subtotal thyroidectomy 1953
28	F	5	1954	¼	Mixed papil. and follic. ca.	None	..	Living and well 1954
Group C. Carcinoma of Thyroid with Metastasis to Cervical Lymph Nodes Treated by External Irradiation Only								
29	F	9	1924	2	Mixed papil. and follic. ca.	X-ray, 18 yr.	21	Biopsy of cervical node 1924; died 1945; chest metastases 1943
30	F	8	1934	½	Mixed papil. and follic. ca.	X-ray and radium, many yr.	18	Biopsy 1934 and 1937; questionable metastasis to bone 1937; myxedema; actinodermatitis; untraced since 1952; palpable cervical node 1952
31	F	13	1940	5	Papil. ca.	X-ray, many yr.	14	Biopsy (E) 1939; metastatic cervical lymph node 1954; living and well 1954

TABLE 1.—*Carcinoma of the Thyroid Gland in Children: Classification of Cases* *—Continued

Case	Sex	Age, Yr.	Yr. Seen	Duration, Yr.	Pathologic Diagnosis	Nonsurgical Treatment	Follow-up, Yr.	Comment
Group D. Extensive Carcinoma of Thyroid Treated by Total Surgical Thyroidectomy								
32	F	14	1952	10	Solid ca., Gr. 2	X-ray, 1952	2	Myxedema and hypoparathyroidism; no recurrence 1954
33	F	5	1953	1	Mixed papil. and follic. ca.	None	1	Previous subtotal thyroidectomy 1953 (E); cervical nodes removed 1953; myxedema and hypoparathyroidism; no recurrence 1954
34	M	12	1954	1/10	Mixed papil. and follic. ca.	I^{131}	..	Recurrence in neck; chest metastasis; myxedema and hypoparathyroidism; currently being treated
35	M	11	1954	2½	Follic. ca.	I^{131}	..	Left vocal-cord paralysis; tracheotomy; myxedema and hypoparathyroidism; currently being treated
Group E. Inoperable Carcinoma of Thyroid								
36	F	9	1926	½	Mixed papil. and follic. ca.	Radium	11	Respiratory obstruction for several years; myxedema; died 1937; chest metastases 1932
37	F	13	1932	6	Papil. ca.	X-ray and radium	6	Untraced since 1938; living and well 1938
38	F	10	1936	7	Papil. ca.	Radium	15	Metastasis to lung 1951, but well; actinodermatitis; untraced since 1951
39	M	6	1942	1½	Mixed papil. and follic. ca.	Radium and x-ray	7	Metastasis to chest and cervical and mediastinal nodes; actinodermatitis; died 1949; respiratory difficulty for years
40	F	10	1947	½	Mixed papil. and follic. ca.	Radium 1947; I^{131} 1949	6	Myxedema; depression of hemopoietic system after I^{131}; living and well 1953
41	F	12	1947	3	Follic. ca.	X-ray 1947; I^{131} 1948	6	Myxedema; palpable cervical nodes 1953; living and well 1953

* (E) indicates treatment given elsewhere.

CLASSIFICATION OF CASES

The 41 patients in this study have been divided arbitrarily into five groups based on the primary type of treatment that each received at the time of the original visit to the clinic. The relatively small number of patients, the difference in the degree of involvement by carcinoma, and the great variability in the types of treatment used make it apparent that no truly satisfactory grouping of these patients is possible (Table 1).

The seven patients in Group A manifested no evidence of metastatic spread of the carcinoma clinically or at the time of operation. In each case the tumor appeared to be confined to a lobe of the thyroid, and it was considered completely excised by the surgeon. All patients received postoperative roentgen-ray or radium therapy. One patient in this group had recurrent thyroid carcinoma in the cervical lymph nodes and metastasis to the lungs, and died in 1950, twenty years after the diagnosis of carcinoma of the thyroid had been established.

The 21 patients comprising Group B were, for the most part, seen initially by a physician because of enlarged cervical lymph nodes. In 14 of these, the diagnosis was established before arrival at the clinic by biopsy of a cervical lymph node or at the time of subtotal thyroidectomy. Nineteen patients presented evidence of carcinoma involving only one lobe of the thyroid, with metastasis to the cervical lymph nodes on the same side.

All the patients in Group B were subjected to subtotal thyroidectomy. In 15 patients the involved lobe of the thyroid, the isthmus, and the nodes were removed. In the other six, both lobes were partially removed, together with the isthmus and involved lymph nodes. Two patients had a second subtotal resection, while one had three subtotal resections. Nine patients have had resection of lymph nodes involved by metastatic carcinoma subsequent to the original operation. Three patients underwent tracheotomy, and twelve received radiotherapy.

There have been two deaths among the patients of Group B. One died of thyroid carcinoma one year after the diagnosis was established and three years after the onset of symptoms. The second patient was subjected to subtotal thyroidectomy in 1908, 1913, and 1917. In 1919 she returned to the clinic because of hypertension and nephritis complicating pregnancy. She was not seen again but wrote that she was well in December, 1926. In 1927 we received word of her death; unfortunately, we have not been able to determine the cause of death.

The three patients in Group C were treated with roentgen rays or radium alone, at least early in the course of the disease. One died 21 years after the diagnosis of carcinoma of the thyroid was established. The other two are living, and both have enlarged cervical lymph nodes which probably are the site of metastatic carcinoma. One of the living patients had lesions in the spinal column and skull three years after the diagnosis of carcinoma had been established. Roentgen therapy was administered over the involved areas of bone and healing occurred promptly. The nature of the pathologic changes in the bones was not proved, but the lesions were assumed to be the result of metastatic carcinoma from the thyroid. The patient was living and well when last heard from, in 1952, eighteen years after the diagnosis of carcinoma was established.

Group D includes four patients seen during the past two years, each with extensive carcinoma of the thyroid. Total thyroidectomy with removal of cervical lymph nodes was done in each case. Two of the patients have not manifested evidence of residual carcinoma and therefore have not been given additional treatment. The other two patients have shown evidence of residual carcinoma according to the observations of the surgeon or the results of radioiodine-uptake studies and therefore are being treated with radioiodine.

The six patients in Group E were considered to have inoperable carcinoma of the thyroid at the time of original study at the clinic. All were treated with radioiodine, radium, or roentgen rays. Extensive infiltration of the nerves, trachea, or esophagus and metastasis to the lungs were the criteria by which the tumors were adjudged inoperable. Two patients are known to have died, one 7 and the other 11 years after the diagnosis was established.

PATHOLOGIC CHARACTERISTICS

All the thyroid carcinomas in this series were of the slowly growing type, with a corresponding low grade of histologic malignancy. There were no cases of Hürthle-cell carcinoma, anaplastic carcinoma, or lymphosarcoma in this series.

In 36 of the 41 cases the disease was classified as papillary and follicular carcinoma, a type that is commonly associated with metastasis to the regional nodes. In 7 of the 36 cases the lesions were of predominantly papillary structure, with little or no follicular component (Fig. 4*a*), while in 8 cases they were predominantly follicular in structure, with abundant colloid formation and a small papillary element (Fig. 4*b*); in the remaining 21 cases the lesions were of the mixed papillary and follicular type. Papillary carcinomas with an associated nonglandular solid component were included in the mixed type. From this small series no conclusion can be drawn with respect to differences in biologic behavior of these structural types. Regional lymph nodes were involved in 33 of the 36 carcinomas, and in 32 cases the presenting symptom was metastasis to lateral nodes in the neck. As in lesions in adults, the primary tumor was frequently small as compared to the size of the metastatic deposit. The most striking example of "lateral aberrant thyroid" was that of a primary thyroid lesion, 3 mm. in diameter, with two associated metastatic lesions in lymph nodes, the larger of which measured 4 cm. in diameter. Pulmonary metastasis was noted during the course of the disease in seven patients, of whom one had papillary carcinoma and six had mixed papillary and follicular carcinoma. Metastasis to bone was suspected in one patient with mixed type of carcinoma.

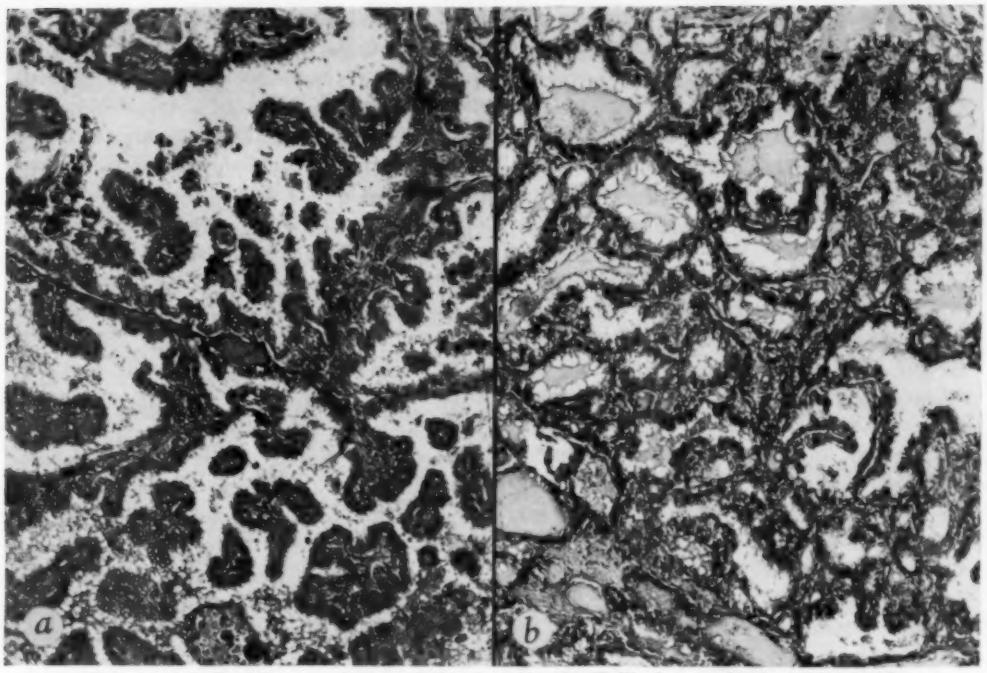
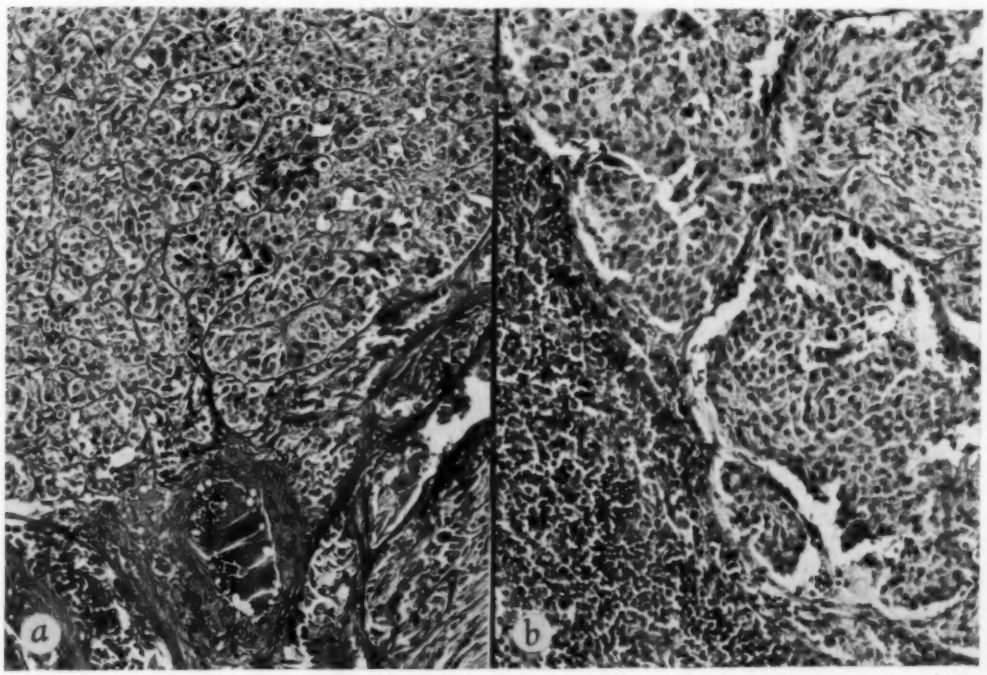


Fig. 4.—(*a*) Papillary carcinoma of the thyroid. (*b*) Follicular carcinoma with abundant production of colloid.

Fig. 5.—Encapsulated solid and follicular carcinoma. (*a*) Primary lesion showing predominantly solid and trabecular pattern. (*b*) Metastatic lesion to a lymph node in another case, showing solid structure.



The second type of tumor found in the remaining five cases was the encapsulated carcinoma, frequently referred to as "malignant adenoma." In this group, as in corresponding tumors of adults, there occur certain borderline lesions in which histologic diagnosis is difficult. The diagnosis of malignancy in this group is based on such features as nuclear anaplasia, the presence of mitotic figures, extension beyond the capsule, and invasion of blood vessels. Of the five tumors in this group, three were histologically follicular or solid in structure and of low-grade malignancy (Grade 1). The other two were of a predominantly solid structure, with little or no follicular component and of a moderate degree of histologic malignancy (Grade 2) (Fig. 5*a* and *b*); extension beyond the capsule was demonstrated in both, and nodal metastasis occurred in one. Vascular invasion was noted in one of the five. Distant metastasis was demonstrated in one of the five patients 20 years after the diagnosis was first established.

TREATMENT

Surgical Treatment.—The treatment of thyroid carcinoma in children is similar to that in adults. The treatment of choice is surgical, if on clinical examination the lesion is thought to be operable. Even if there is some question about operability, all lesions should at least be explored and a satisfactory biopsy specimen obtained for histologic study. In the presence of nodular goiter, whether the lesion is suspected of being a carcinoma or not, the lateral cervical region should be examined carefully for clinical evidence of metastasis in the effort to choose the proper surgical procedure.

The thyroid gland should be explored through the usual collar incision. After the strap muscles have been spread and retracted laterally, the thyroid gland is exposed and any tumor carefully examined. If there is gross evidence of carcinoma, the surgeon is then justified in proceeding with total lobectomy on the side of the lesion, taking precautions to preserve the recurrent laryngeal nerve. The tracheoesophageal nodes are the ones most frequently involved in the presence of papillary carcinoma of the thyroid gland; hence, they should always be explored and removed if indicated. The midjugular and the lower deep jugular group of nodes are the next most commonly involved. Metastatic lesions are sometimes seen in the upper deep jugular group of nodes. Unless there is massive nodular involvement in the lateral part of the neck, we do not consider radical dissection of the neck warranted in the treatment of this type of carcinoma but prefer a modified cervical dissection, excising the involved nodes or groups of nodes and node-bearing tissue.

Metastatic papillary carcinoma from the thyroid tends to remain encapsulated for long periods. On occasion it has been necessary to excise another node or group of nodes when metastasis has become apparent at some time after the initial spread. Rarely is a third such operation indicated. If nodes are not palpable in the neck and none are discovered at the time of operation, the contents of the lateral part of the neck are not disturbed. Of 174 papillary carcinomas of the thyroid representing all age groups and treated with these thoughts in mind, none became inoperable because of inadequate treatment of cervical metastatic lesions.* Because of this experience we believe that radical dissection of the neck is not indicated in the great majority of patients with papillary carcinoma of the thyroid. In the present series of children, radical dissection of the neck was not considered indicated in a single instance.

If the carcinoma is well localized, only partial lobectomy is performed on the contralateral side in addition to lobectomy on the affected side. The partial lobectomy not only preserves thyroid tissue for normal metabolic function but protects the corresponding parathyroid glands. If the carcinoma is located in the isthmus of the thyroid gland, then subtotal thyroidectomy should be done, leaving a remnant on either side equal to less than one-fourth of a normal lobe.

* Unpublished data.

When distant or local metastasis or extension of the primary tumor makes the lesion inoperable, the surgeon is still justified in considering and performing, if possible, a total thyroidectomy. This facilitates possible treatment of the remaining carcinoma by radioactive iodine. In the absence of all thyroid tissue, some carcinomas will function sufficiently to accumulate therapeutic amounts of radioactive iodine. Total surgical thyroidectomy is frequently followed by parathyroid insufficiency, a complication which is serious enough to contraindicate this procedure unless the seriousness of the carcinoma makes it specifically indicated.

Treatment with Radioactive Iodine.—As already indicated, the preferred treatment of carcinoma of the thyroid gland in children is surgical excision whenever possible. In patients with inoperable or metastatic thyroid carcinoma, radioactive iodine may be useful as a therapeutic agent. The successful use of this agent depends upon the ability of the carcinoma to accumulate iodine in sufficient concentrations to be lethal to the malignant cells. At the same time the amount of radioiodine given must be small enough to avoid severe radiation injury to the hemopoietic system. One patient among those in the group treated with radioactive iodine developed marked depression of the bone marrow, followed by slow but finally complete recovery.

In an effort to increase the accumulation of radioactive iodine by thyroid carcinoma, certain techniques have been tried. Normal thyroid tissue usually accumulates iodine more readily than does carcinoma tissue; therefore it is necessary to remove the normal thyroid tissue which is competing with the carcinoma tissue for the administered I^{131}. Removal of the normal thyroid tissue theoretically has the additional advantage of increasing production of endogenous thyrotropin as a result of producing hypothyroidism. We have been unable to demonstrate an increased accumulation of radioiodine by carcinoma of the thyroid following the administration of exogenous thyrotropic hormone.

The normal thyroid may be removed by one of two methods, both of which have disadvantages. The surgeon may elect to do a total thyroidectomy at the time of the original exploration of the thyroid if it is impossible to remove the carcinoma completely. This operation may be technically difficult and is usually followed by hypoparathyroidism. Alternatively, normal thyroid tissue may be destroyed by the administration of radioactive iodine. The disadvantage of this type of treatment is that a relatively large total dose of radioactive iodine may be necessary to destroy both the normal thyroid tissue and the carcinoma.

The ability of the carcinoma of the thyroid to accumulate I^{131} may be estimated in several ways. Solid and papillary carcinomas usually have little or no ability to accumulate iodine, while tumors of follicular structure usually are more prone to form colloid and to accumulate iodine. This is best demonstrated by a review of our experience with autoradiograms made on 19 patients seen since 1947 (Table 2).

TABLE 2.—*Carcinoma of the Thyroid Gland in Children: Results of Autoradiographic Examination (Nineteen Cases)*

Type of Carcinoma	Total Patients	Accumulation of I^{131}		
		None	Fair to Moderate	Good
Mixed papillary and follicular	12	6*	3	3
Predominantly follicular	3	0	2	1
Predominantly papillary	3	3	0	0
Solid	1	1	0	0

*In one case a primary carcinoma removed in 1952 showed no evidence of radioiodine accumulation, but a node containing metastatic thyroid carcinoma removed in 1954 showed marked avidity for radioiodine.

In the absence of normal thyroid tissue the iodine-accumulating ability of thyroid carcinoma is best estimated by the administration of a tracer dose of radioactive iodine. The amount of I^{131} accumulated in the neck or in metastatic growths may be measured directly. At the same time the total I^{131} retained may be estimated by measuring the percentage of the total dose excreted in the urine during the 24 or 48 hours after administration of the test dose.

Radioactive iodine was used as a therapeutic agent in only five children in this series. Two of the patients were treated with I^{131} in three divided doses over a period of approximately nine months. The first dose in each case was given with the idea of destroying the normal thyroid tissue. They received a total of 119.5 and 175 mc. of I^{131}, respectively. A third patient was given 50 mc. of I^{131} after subtotal resection of the thyroid, when the autoradiogram indicated the carcinoma had a marked avidity for radioiodine. The remaining two patients given radioiodine as a therapeutic agent were noted to have evidence of residual carcinoma, as indicated by I^{131} tracer studies made after total surgical thyroidectomy. These patients have been given 226 and 60 mc. of I^{131}, respectively, and both are still under treatment.

Roentgen-Ray and Radium Therapy.—Roentgen rays and radium are of definite value in the treatment of certain children with carcinoma of the thyroid. The value of these agents is attested by others [5] and is amply confirmed by our own observations. The patients in this series treated with external radiation have for the most part been treated with tumor doses which, by present concepts, would be considered low or moderate in amount.

There has been a definite change in our policy regarding the use of external irradiation. Prior to 1950 it was our practice to treat all carcinomas of the thyroid with external irradiation after operation even though the surgeon may have been confident that all of the carcinoma was removed at the time of operation. We no longer give postoperative irradiation as a routine, since we believe local recurrences can, in most cases, be best treated by surgical excision. Those patients who have recurrences that are not amenable to surgical removal should be treated with radiation. If the carcinoma can be made to concentrate I^{131} in sufficient amount, treatment can be given with radioactive iodine. If there is little or no concentration of I^{131} in the tumor, external irradiation with roentgen rays is the preferable treatment.

An occasional patient with extensive localized carcinoma of the thyroid may be treated satisfactorily with external irradiation even though the tumor has the ability to accumulate radioiodine.

Results of Treatment.—There was no operative death in this series of patients. Six patients are known to have died 21, 20, 18, 11, 7, and 1 years, respectively, after the diagnosis of carcinoma of the thyroid was established. Five of the six are known to have had widespread carcinoma with metastatic lesions in the lungs. The sixth patient is considered to have died of thyroid carcinoma, although she also had chronic nephritis and hypertension. Postmortem examinations were not done here on any of the patients.

TABLE 3.—*Carcinoma of the Thyroid Gland in Children: Survival Data* *

Period, Yr.	Patients		Lived Beyond Indicated Period	
	Total	Traced	No.	Per Cent of Traced Patients
3	31	30	29	96.7
5	23	21	20	95.2
10	17	14	12	85.7
15	13	11	9	81.8
20	8	5	3	60.0

* Inquiry as of Jan. 1, 1955.

Data on survival are summarized in Table 3. Of particular interest is the fact that two patients died of carcinoma of the thyroid 20 and 21 years, respectively, after diagnosis, and one patient is still living 24 years after diagnosis.

Metastatic involvement of the lungs is known to have occurred in eight patients, including five of those who died. Metastasis to bone was not proved in any patient but was suspected in one. Metastasis to the cervical lymph nodes is known to have occurred in 35 of the 41 patients.

Hypothyroidism developed in 13 patients, but in 6 of these it was induced as a part of the plan of treatment. Hypoparathyroidism occurred in all four patients subjected to total surgical thyroidectomy. Actinodermatitis of the neck developed in three patients

treated for long periods with radium or roentgen rays. Occasionally a keloid developed in the operative scar.

SUMMARY AND CONCLUSIONS

Carcinoma of the thyroid gland among children less than 15 years of age is a relatively rare condition which has been recognized at the Mayo Clinic in only 41 children since 1909. It has been reported approximately 250 times. Girls are affected more frequently than boys, the ratio being about two to one. A nodular lesion of the thyroid gland and discrete, firm, nontender cervical lymph nodes not associated with evidence of infection should always suggest the possibility of carcinoma of the thyroid. The diagnosis is established only by histologic examination of the tissue removed at biopsy. Satisfactory treatment depends on several factors which are outlined in the light of experience with the disease in this series of cases. Carcinoma of the thyroid gland among children is almost always a slow-growing neoplasm, although metastatic lesions appear early and may be extensive at the time the disease is recognized. A satisfactory response may be expected to follow appropriate therapy. Anaplastic neoplasms of the thyroid gland have not been encountered among children at the Mayo Clinic. There have been 6 deaths among the 41 patients of this series.

REFERENCES

1. Pemberton, J. deJ., and Black, B. M.: Symposium on Surgical Lesions of Thyroid: Goiter in Children, Surgery. **16**:756-763 (Nov.) 1944.

2. Kennedy, R. L. J.: Nodular Goiter Among Infants and Children, Tr. Am. A. Study Goiter, pp. 322-326, 1940.

3. Winship T., and Chase, W. W.: Childhood Thyroid Carcinoma in Western Europe, Arch. chir. neerl. **5**:253-261, 1953.

4. Winship, T.: Symposium on Thyroid Tumors: Carcinoma of the Thyroid in Children, Tr. Am. Goiter A. (1951), pp. 364-389, 1952.

5. Warren, S.; Alvizouri, M,. and Colcock, B. P.: Carcinoma of the Thyroid in Childhood and Adolescence, Cancer **6**:1139-1146 (Nov.) 1953.

News and Comment

ANNOUNCEMENTS

Courses in Cardiac Problems and in Treatment of Poisonings.—Courses in the most modern and practical means of treating children with cardiac problems and recent advances in the diagnosis and treatment of poisonings, will be offered by the New York University Post-Graduate Medical School during the month of December.

Recent Advances in the Diagnosis and Treatment of Poisonings will be presented for three days, full time, from Dec. 5 through 7. Designed for the practicing physician, the course will cover the newer methods of treatment combining physiological and chemical antidotes. Actual testing of materials will be undertaken in the laboratories of the Chief Medical Examiner and the Toxicologist of the City of New York.

Pediatric Cardiology consists of five days of full-time instruction, beginning Dec. 5. It will include an intensive review of the most recent advances of pediatric cardiology and the various diagnostic and therapeutic procedures.

For further information write to Dean, NYU Post-Graduate Medical School, 550 First Ave., New York 16.

Fellowships in Pediatric Rehabilitation.—The Children's Division of the Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, announces the availability of two fellowships in pediatric rehabilitation for pediatricians.

These fellowships are made possible by funds supplied by the Association for the Aid of Crippled Children. Training will be offered in the rehabilitation of children with disabilities resulting from neuromuscular, muscular, and orthopedic conditions.

The fellowship stipend is $4000, and the training period is one year, beginning Jan. 1 or July 1, 1956.

Further information can be obtained by writing George G. Deaver, M.D., Director, Children's Division, Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, 400 E. 34th St., New York 16.

Scientific Exhibits

CONGENITAL AGANGLIONIC MEGACOLON

Hirschsprung's Disease

JOHN F. MOKROHISKY, M.D.
AND
GEORGE P. KEEFER, M.D.
PHILADELPHIA

CONGENITAL megacolon was recognized as a clinical entity in 1887, following Hirschsprung's comprehensive analysis of two patients with this disease. Up until a few years ago the term "Hirschsprung's disease" had been used to describe enlargement of the colon in those patients not having demonstrable organic cause for their megacolon.

In 1920 the first comprehensive study of the ganglion cells of a colon from a patient with Hirschsprung's disease was made by Dalla Valle. He reported the absence of ganglion cells in the narrowed segment of bowel distal to the dilated colon.

In 1949 Neuhauser described a technique of barium-enema examination for demonstrating the narrowed, aganglionic segment. Following this noteworthy contribution, Swenson described an operative technique for removal of the abnormal segment and restoration of the continuity of the bowel with preservation of the anal sphincters.

In this exhibit, special emphasis is directed to the variations in the roentgenographic appearances of the abnormal aganglionic segments as revealed by the barium-enema examination. Recognition of these various roentgenographic types of aganglionic segments is essential for accurate diagnosis. The exhibit is based on a study of 44 cases of congenital aganglionic megacolon.

Submitted for publication July 13, 1955.

Shown as a scientific exhibit of the Section on Pediatrics at the 104th Annual Meeting of the American Medical Association, Atlantic City, N. J., June 6-10, 1955.

From the Departments of Radiology, St. Christopher's Hospital for Children and Temple University Hospital and School of Medicine. Dr. Mokrohisky is now at Our Lady of Lourdes Memorial Hospital, Binghamton, N. Y.

Dr. James B. Arey (St. Christopher's Hospital for Children) gave assistance in reviewing the pathological findings, and Dr. Samuel L. Cresson (St. Christopher's Hospital for Children) gave permission for the use of the clinical records and surgical observations in most of the patients. Dr. John W. Hope (the Children's Hospital of Philadelphia) gave permission for review of the films on 17 cases of Hirschsprung's disease and the reproduction of films from Cases 40, 42, and 43. Figures 1-15 were reproduced from Keefer, G. P., and Mokrohisky, J. F.: *Radiology* **63**:157-175 (Aug.) 1954, with permission of the Radiological Society of North America, Syracuse, N. Y. This article included a study of our initial 18 cases.

CONGENITAL AGANGLIONIC MEGACOLON

CLASSIFICATION OF MEGACOLON

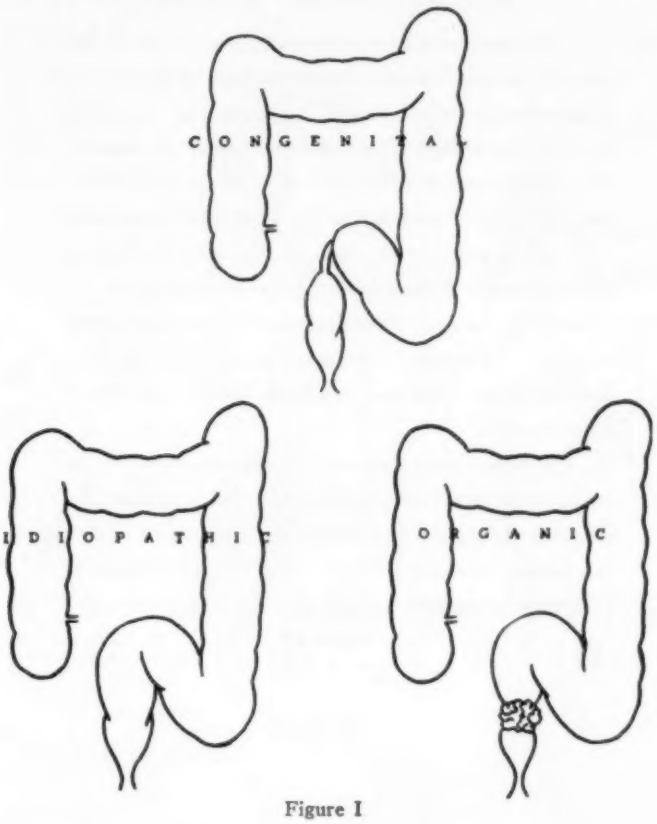


Figure I

HIRSCHSPRUNG'S DISEASE

CLASSIFICATION OF MEGACOLON

CONGENITAL MEGACOLON OR "HIRSCHSPRUNG'S DISEASE" IS DUE TO A FUNCTIONAL OBSTRUCTION PRODUCED BY A NARROWED SEGMENT OF COLON DEVOID OF GANGLION CELLS. THE PRIMARY DISTURBANCE IS AN INTERFERENCE WITH THE PASSAGE OF PERISTALTIC WAVES ACROSS THE AGANGLIONIC SEGMENT RESULTING IN THE INEFFECTIVE PROPULSION OF COLONIC CONTENTS ACROSS THE INVOLVED SEGMENT WITH SECONDARY DILATATION OF THE COLON PROXIMAL TO THIS AREA. SYMPTOMS OF CONGENITAL MEGACOLON BEGIN AT BIRTH OR DURING THE FIRST FEW WEEKS OF LIFE WITH CONSTIPATION, PROGRESSIVE ABDOMINAL DISTENTION AND VOMITING. THE MORTALITY OF UNTREATED CASES IS HIGH. THE DIAGNOSIS IS MADE BY DEMONSTRATING THE NARROWED SEGMENT OF BOWEL BY BARIUM ENEMA EXAMINATION.

Figure II

HIRSCHSPRUNG'S DISEASE

CLASSIFICATION OF MEGACOLON

IDIOPATHIC MEGACOLON HAS NO DEFINITE ETIOLOGICAL BASIS. AMONG THE CONTRIBUTING FACTORS ARE: FAULTY BOWEL HABITS, SPASTIC SPHINCTER OR EXCESSIVE WATER ABSORPTION FROM AN UNUSUALLY ELONGATED SIGMOID. SYMPTOMS OF CONSTIPATION ARE NOT PRESENT FROM BIRTH. THE ONSET OF SYMPTOMS IS SLOW AND THE MORTALITY IS LOW. THE DIAGNOSIS IS MADE BY EXAMINATION OF THE LARGE BOWEL BY A BARIUM ENEMA WHICH SHOWS DILATATION OF THE COLON ALL THE WAY TO THE ANUS.

ORGANIC MEGACOLON MAY OCCUR AT ANY AGE. THE OBSTRUCTING LESION MAY BE A TUMOR, STRICTURE, CONGENITAL BAND OR OTHER PATHOLOGIC PROCESS WHICH CAN BE DEMONSTRATED GROSSLY.

Figure III

HIRSCHSPRUNG'S DISEASE

ROENTGENOGRAPHIC FINDINGS

THE NARROWED SEGMENT VARIES FROM 2 TO 25 CM. IN LENGTH. LONGER NARROWED SEGMENTS MAY BE ENCOUNTERED IN APPROXIMATELY 10% OF CASES. USUALLY THE TRANSITION BETWEEN THE NARROWED AND DILATED SEGMENTS IS ABRUPT, BUT IN SOME CASES THE CHANGE IS MORE GRADUAL SO THAT THE TRANSITIONAL ZONE IS "FUNNEL-SHAPED" IN APPEARANCE

IN THE MAJORITY OF CASES THE TRANSITIONAL ZONE AS SEEN FLUOROSCOPICALLY AND ROENTGENOGRAPHICALLY REPRESENTS THE MOST PROXIMAL PART OF THE AGANGLIONIC SEGMENT THE ENTIRE AGANGLIONIC SEGMENT MAY BE CONTRACTED; MORE COMMONLY, HOWEVER, ONLY A PART OF IT IS CONTRACTED

WE HAVE FOUND THE DOUBLE CONTRAST STUDY OF THE COLON TO BE OF DEFINITE DIAGNOSTIC VALUE IN DEMONSTRATING THE NARROWED SEGMENT IN THOSE INSTANCES WHERE THE BARIUM CONTRAST FINDINGS, USING THE SLOW FILLING TECHNIQUE, WERE INCONCLUSIVE FOR DIAGNOSIS

Figure IV

HIRSCHSPRUNG'S DISEASE

ROENTGENOGRAPHIC FINDINGS

THE ROENTGENOGRAPHIC APPEARANCE OF THE AGANGLIONIC SEGMENT MAY SHOW ONE OF THE FOLLOWING VARIATIONS.

TYPE I. THE PROXIMAL PART OF THE AGANGLIONIC SEGMENT MAY BE CONTRACTED WHEREAS THE DISTAL PART MAY BE RELATIVELY NORMAL IN SIZE. (FIGURES 5B AND 7).

TYPE II. THE ENTIRE AGANGLIONIC SEGMENT MAY BE MARKEDLY CONTRACTED. (FIGURES 8, 9A AND 10).

TYPE III. A RELATIVELY SHORT SEGMENT OF ANNULAR SPASM. (FIGURES 11, 12 AND 13).

TYPE IV. THE AGANGLIONIC SEGMENT MAY SEEM TO BE NORMAL BUT WHEN COMPARED WITH THE DILATED BOWEL ABOVE THERE IS A MARKED DIFFERENCE IN CALIBRE. (FIGURES 14A AND 14B).

TYPE V. TWO AREAS OF SPASM SEPARATED BY A NORMAL SEGMENT OF BOWEL. (FIGURE 15) (DOUBLE ZONAL AGANGLIA).

Figure V

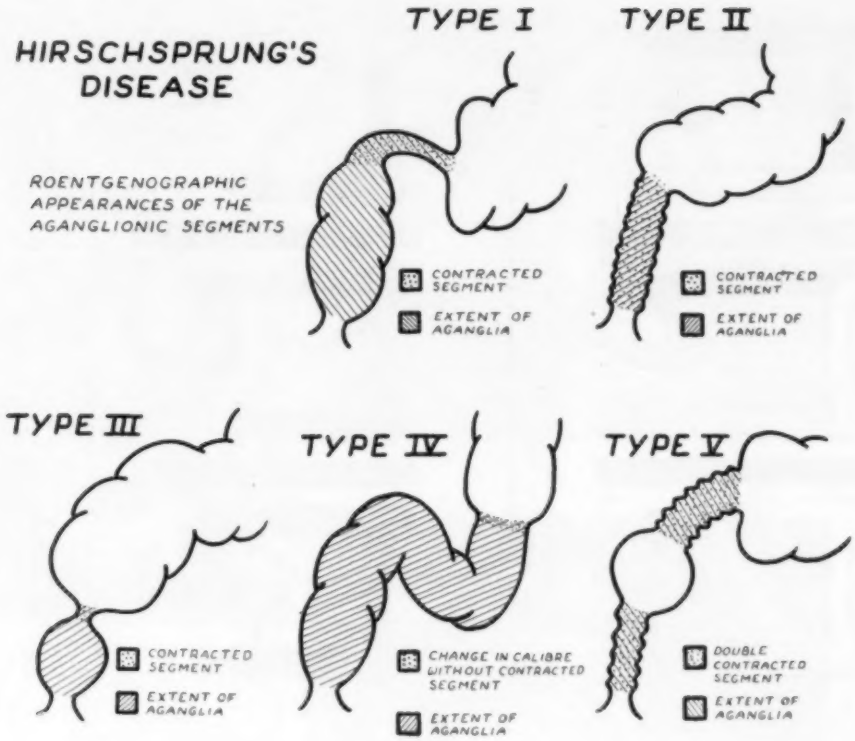


Figure VI

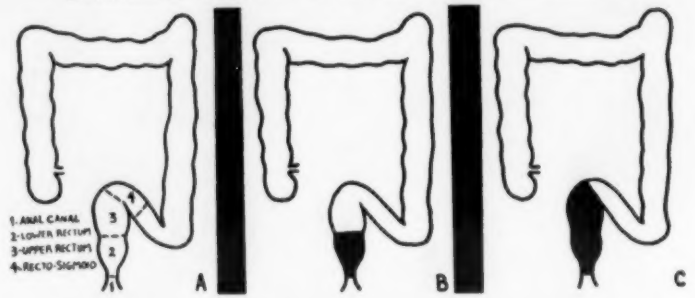
INCIDENCE OF ROENTGENOGRAPHIC TYPE OF AGANGLIONIC SEGMENT

	CASES	PERCENTAGE
TYPE I	12	28%
TYPE II	20	48%
TYPE III	5	12%
TYPE IV	4	10%
TYPE V	1	2%

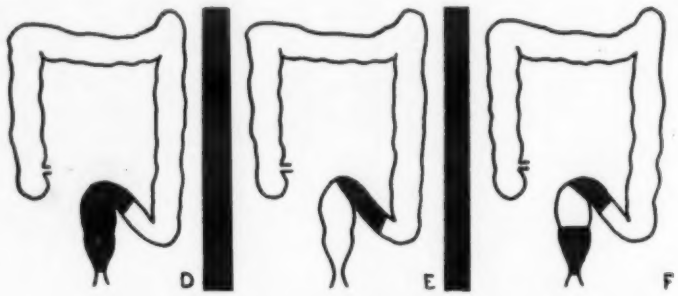
Figure VII

HIRSCHSPRUNG'S DISEASE

LOCATIONS OF VARIOUS TYPES OF SHORT AGANGLIONIC SEGMENTS



Schematic drawings of: (A) normal colon; (B) segment of aganglia in the lower rectum; (C) segment of aganglia involving the entire rectum.

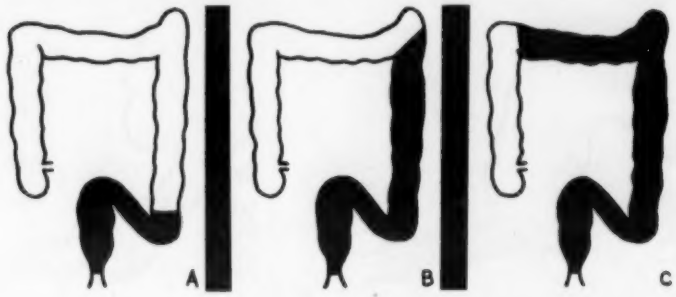


(D) segment of aganglia involving the entire rectum and recto-sigmoid. This is the most frequent site of involvment. (E) segment of aganglia in the sigmoid. Ganglia present above and below the involved segment ,single zonal aganglia). (F) segments of aganglia in the recto-sigmoid and in the lower rectum(double zonal aganglia). Ganglia present in the upper rectum and proximal to the recto-sigmoid.

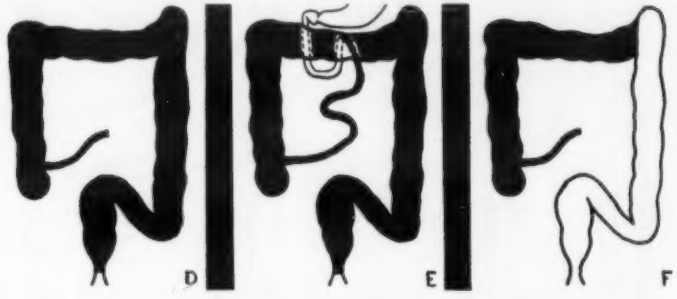
Fig. 1.—Hirschsprung's disease. Locations of various types of short aganglionic segments. The schematic drawings above merely represent the various locations of short aganglionic segments. They do not necessarily indicate the "extent of narrowing" seen roentgenographically.

HIRSCHSPRUNG'S DISEASE

LOCATIONS OF VARIOUS TYPES OF LONG AGANGLIONIC SEGMENTS



Schematic drawings of: (A) segment of aganglia from distal descending colon to anus. (B) segment of aganglia from splenic flexure to anus. (C) segment of aganglia from hepatic flexure to anus.



Variants of Hirschsprung's Disease- absence of megacolon: (D) segment of aganglia from distal ileum to anus. (E) segment of aganglia from duodeno-jejunal junction to anus. (F) segment of aganglia from the distal ileum to the splenic flexure. Ganglia present proximal to the involved distal ileum and distal to the splenic flexure.

Fig. 2.—Hirschsprung's disease. Locations of various types of long aganglionic segments. The schematic drawings above merely represent the various locations of long aganglionic segments. They do not necessarily indicate the "extent of narrowing" seen roentgenographically.

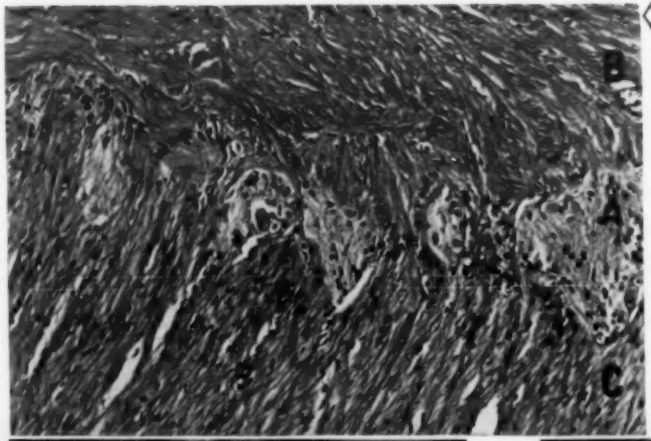


Fig. 3 (Case 18).—Hirschsprung's disease. Histologic section from dilated segment of colon. *A*, intramural plexus in dilated segment of colon with normal ganglion cells; *B*, longitudinal muscle; *C*, circular muscle. Reduced ⅓ from mag. × 200.

Fig. 4 (Case 18).—Hirschsprung's disease. Histologic section from narrowed segment of colon. Absence of intramural plexus in the aganglionic segment. (Compare with normal myenteric plexus seen in Figure 3.) *A*, usual site of myenteric plexus; *B*, longitudinal muscle; *C*, circular muscle. Reduced ⅓ from mag. × 200.

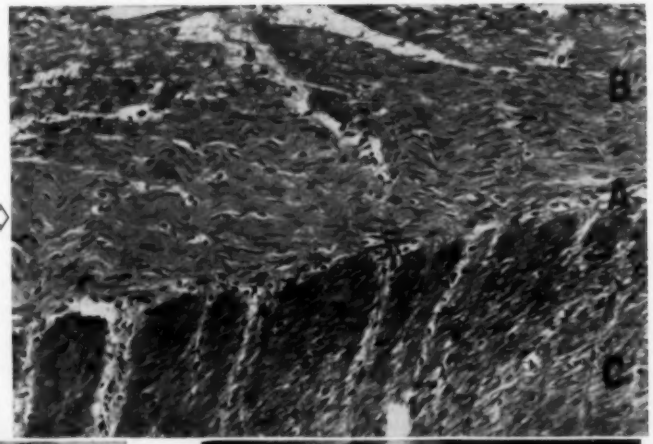


Fig. 5 (Case 7).—Hirschsprung's disease. (*A*), B. W., 7-year-old white girl, had a history of constipation since birth. Admitted to the hospital because of vomiting two to three times a day, of one month's duration. Roentgenogram of the abdomen shows extreme dilatation of the colon with feces.

Fig. 5 (Case 7, B. W.).—Hirschsprung's disease (Type I). (*B*) Barium contrast film shows the area of narrowing in the rectrosigmoid region, which is overlapped by the proximal dilated colon. Note the relatively normal-appearing lower rectum. Insert: Tracing of the barium contrast film shows the corresponding aganglionic segment represented by the white and striped areas.

Fig. 5 (Case 7, B. W.).—Hirschsprung's disease. (*C*), Roentgenogram of the abdomen taken nine months following a Swenson pull-through procedure shows the change to a relatively normal-appearing abdomen. Compare with preoperative film (Fig. 5*A*).

Figure 6

Fig. 6 (Case 5).—Hirschsprung's disease (Type I). L. D., 4-year-old white boy with a history of difficulty in having stools since birth. Bottom: The double-contrast roentgenogram shows the narrowed segment in the sigmoid colon, with a normal-appearing rectum. Note the abrupt transition between the narrowed and the dilated segment. Top: Tracing of roentgenogram indicates the extent of aganglia in white. The normal-appearing rectum also lacks ganglion cells.

Figure 7

Fig. 7 (Case 1).—Hirschsprung's disease (Type I). F. G., 7-year-old white boy with a history of constipation since birth. Admitted to the hospital because of fecal vomiting and signs of intestinal obstruction. Roentgenogram with barium in the distal colon shows a narrowed segment in the rectosigmoid area, with a relatively normal-appearing rectum. Note the dilatation of the colon proximal to the narrowed segment. Insert: Tracing of roentgenogram shows the extent of aganglia in white.

Fig. 9 (Case 4).—Hirschsprung's disease (Type II). *A*, D. N., 4-year-old white boy with a history of constipation since birth. Bottom: Double-contrast roentgenogram shows the area of narrowing distal to the "funnel-shaped" dilated bowel. Top: Tracing of roentgenogram shows the aganglionic segment in white.

Figure 8

Fig. 8 (Case 3).—Hirschsprung's disease (Type II). A. H., one-month-old infant with symptoms of constipation and abdominal distention since birth. Admitted to the hospital because of abdominal distention and paradoxical diarrhea. Bottom: The barium-contrast film shows the spastic segment extending from the rectosigmoid area to the anus. Note the marked dilatation of the colon proximal to the rectosigmoid area. The arrow indicates the transitional zone. Top: Tracing of roentgenogram shows the corresponding aganglionic segment in white.

Fig. 9 (Case 4, D. N.).—Hirschsprung's disease. *B*, Roentgenogram of barium-filled distal colon six months after a Swenson pull-through procedure. Note the normal caliber of the colon. Compare with preoperative film (Fig. 9*A*).

Figure 9

Fig. 10 (Case 2).—Hirschsprung's disease (Type II). *A*, M. W., 3-day-old boy with signs of intestinal obstruction. The narrowed segment was demonstrated by barium enema examination at 2 weeks of age. The double-contrast roentgenogram shows the narrowed segment in the lateral view. The narrowing extends from the proximal sigmoid colon to the anus. Note the "funnel-shaped" transitional zone and the dilatation of the colon proximal to the narrowed segment. Insert: Tracing of roentgenogram shows the extent of aganglia in whtie.

Fig. 10 (Case 2, M. W.).—Hirschsprung's disease (Type II). *B*, Bottom: Barium-contrast films showing the narrowed segment, which includes the entire sigmoid and rectum. Top: Tracing of roentgenogram shows the extent of aganglia in white.

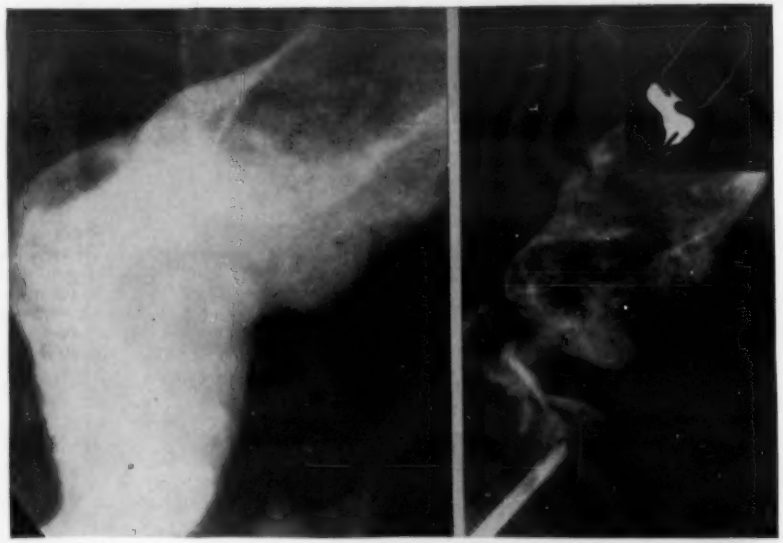


Fig. 11 (Case 8).—Hirschsprung's disease (Type III). A. T., 3-year-old child with a history of alternating diarrhea and constipation since birth. Left: Roentgenogram of barium-filled rectum without any obvious abnormality. Right: Double-contrast film showing an area of spasm in the lower rectum. Insert: Tracing of roentgenogram on the right shows the corresponding aganglionic segment in white.

Fig. 13 (Case 6).—Hirschsprung's disease (Type III). R. H., 7-year-old white boy with a history of chronic constipation and occasional diarrhea. The double-contrast film shows the area of spasm in the lower rectum. The arrows point to the transitional zone which marks the proximal end of the aganglionic segment. Note the dilated colon above the area of spasm.

Fig. 12 (Case 10).—Hirschsprung's disease (Type III). F. S., 7-year-old white girl, admitted to the hospital with the chief complaint of constipation since birth. The double-contrast roentgenogram shows the spastic area in the lower rectum. Insert: Tracing of roentgenogram shows the extent of diminished ganglion cells in white.

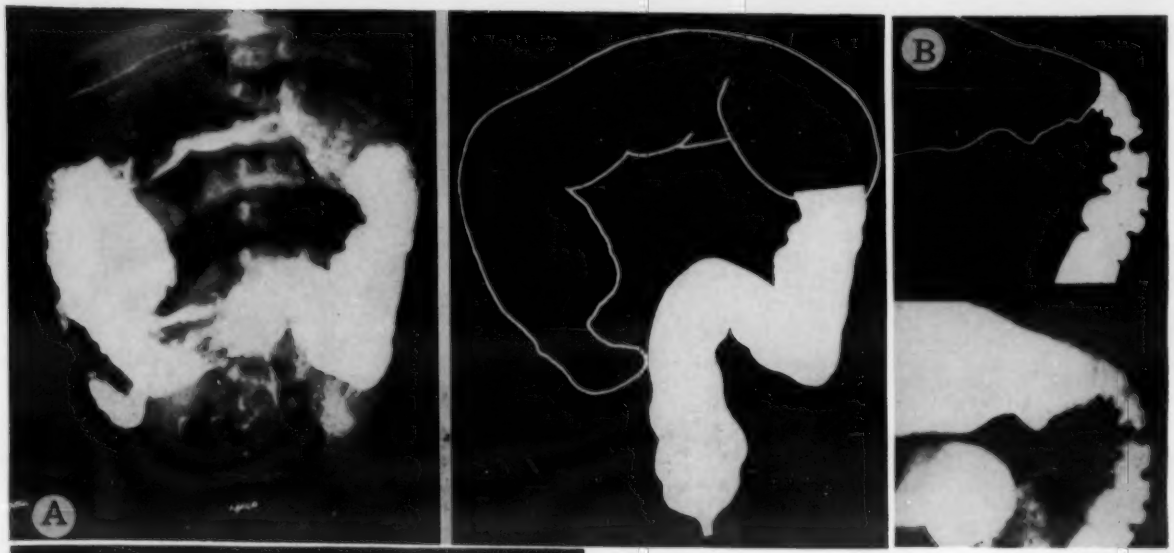


Fig. 14 (Case 12).—Hirschsprung's disease (Type IV). *A*, T. B., one-month-old boy with alternating constipation and diarrhea since birth. Left: Barium-contrast film shows the transition between the relatively normal-appearing descending colon and the dilated transverse colon at the splenic flexure. Right: Tracing of roentgenogram on left shows the extent of aganglia in white, from the splenic flexure to the anus.

Fig. 14 (Case 12, T. B.).—Hirschsprung's disease (Type IV). *B*, Bottom: Spot film roentgenogram of the barium-filled splenic flexure. Note the difference in caliber between the distal transverse colon and the proximal descending colon. Top: Tracing of roentgenogram on bottom shows the corresponding aganglionic segment in white.

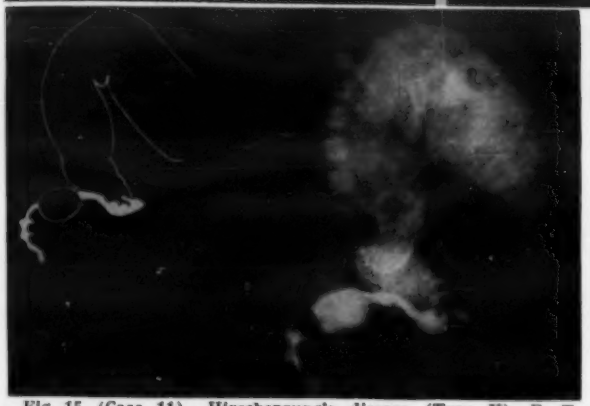


Fig. 15 (Case 11).—Hirschsprung's disease (Type V). R. T., 10-day-old boy, admitted to the hospital because of occasional vomiting and difficulty in having spontaneous bowel movements. Right: Barium-enema roentgenogram shows two areas of narrowing, one in the sigmoid and one in the lower rectum. Note the dilatation of the colon proximal to the sigmoid narrowing. The upper rectum appears normal in caliber. Left: Tracing of roentgenogram on right shows the two zones of aganglia in white, separated by a normal upper rectum, which showed normal myenteric plexuses. This is an unusual case of "double zonal aganglia."

Fig. 16 (Case 40).—Hirschsprung's disease (Type II). E. H., 3-year-old boy with a history of chronic constipation. The barium-contrast film shows the "transitional zone" in the proximal sigmoid. The colon distal to this point is contracted. Note the metallic foreign body in the dilated distal descending colon.

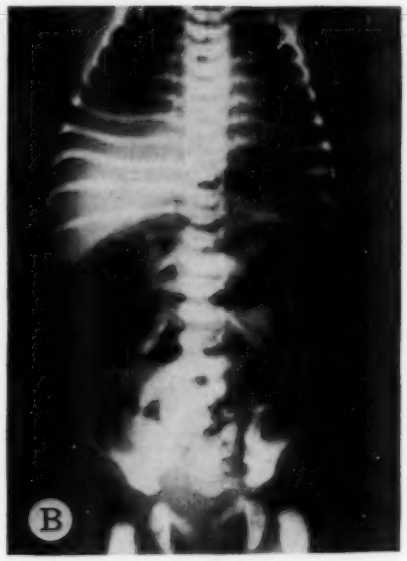
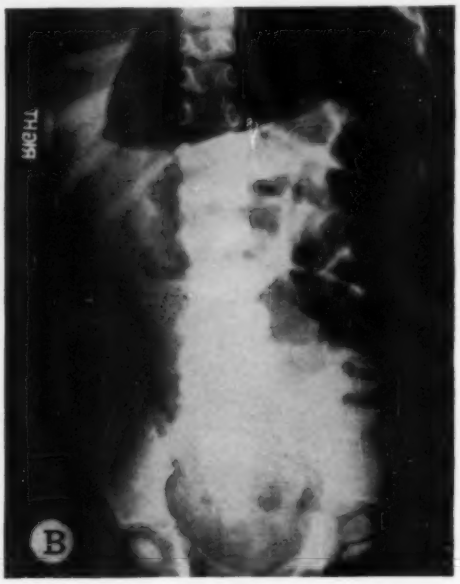


Fig. 17 (Case 42).—Hirschsprung's disease. (*A*) E. S., 3-day-old girl, was admitted with vomiting, abdominal distention, and no stools since birth. The supine film of the abdomen shows considerable air in the small and large intestine. The dilated bowel, in the left lower quadrant and the right upper quadrant, contains considerable meconium.

Fig. 17 (Case 42, E. S.).—Hirschsprung's disease. (*B*) the erect film of the abdomen shows several fluid levels in dilated segments of bowel. The findings were interpreted as partial bowel obstruction due to retained meconium. However, the next roentgenogram shows the true cause of the obstruction as demonstrated by barium-enema examination.

Fig. 17 (Case 42, E. S.).—Hirschsprung's disease (Type II). (*C*) Examination of the colon by contrast material (chloriodized oil [Iodochloral] and iodopyracet [Diodrast]) shows a long, constricted segment extending from the splenic flexure to the anus. The "transitional zone" is clearly seen at the junction of distal transverse colon and proximal descending colon. Histologic sections of the resected narrowed segment disclosed the absence of ganglion cells.



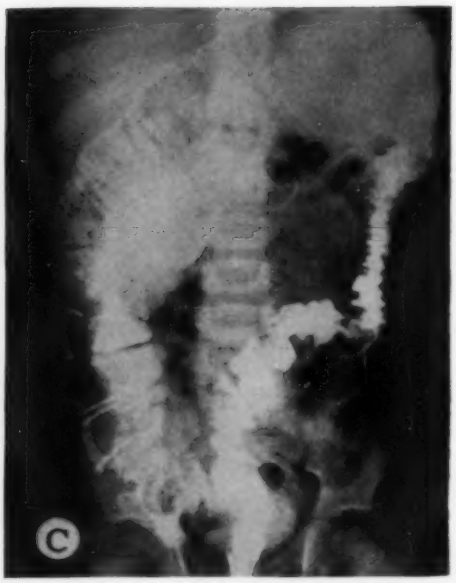


Fig. 18 (Case 43).—Hirschsprung's disease. (*A*) C. S., 3½-year-old white boy, was admitted to the hospital with vomiting and abdominal ditention. History of constipation since birth, necessitating the use of castor oil and enemas. Two brothers of this patient died shortly after birth without passing any meconium or feces, and a half-sister (Case 43) with a history of chronic constipation was found to have an aganglionic segment extending from the recto-sigmoid to the anus. The supine film of the abdomen shows considerable air within the small bowel. The colon is markedly dilated with feces.

Fig. 18 (Case 43, C. S.).—Hirschsprung's disease. (*B*) The erect film of the abdomen shows multiple fluid levels in the small bowel and colon. Considerable air is present in the stomach. The rectum, sigmoid, and right side of the colon contain a huge quantity of liquid fecal material.

Fig. 18 (Case 43, C. S.).—Hirschsprung's disease (Type II). (*C*) the barium-contrast film shows a long, narrowed segment of colon extending from the splenic flexure to the anus. The colon proximal to the splenic flexure is markedly dilated. The entire narrowed segment was found to lack ganglion cells on histologic examination.

CASE	AGE	SEX	ROENTGENOGRAPHIC FINDINGS	PATHOLOGIC FINDINGS
1. FG	7 YRS	M	RECTO-SIGMOID NARROWING	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS
2. MW	2 WKS	M	NARROWING FROM PROXIMAL SIGMOID TO ANUS	NARROWING PROVED AT SURGERY; COLOSTOMY PERFORMED
3. AH	2 MOS	M	NARROWING FROM RECTO-SIGMOID TO ANUS	NARROWING PROVED AT SURGERY; COLOSTOMY PERFORMED
4. DN	4 YRS	M	NARROWING OF UPPER RECTUM	RESECTION; AGANGLIA FROM UPPER RECTUM TO ANUS
5. LD	4 YRS	M	NARROWING OF SIGMOID	RESECTION; AGANGLIA FROM PROXIMAL SIGMOID TO ANUS
6. RH	7 YRS	M	NARROWING IN LOWER RECTUM	RESECTION; SPECIMEN LOST
7. BW	6 YRS	F	RECTO-SIGMOID NARROWING	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS
8. AT	3 YRS	M	NARROWING IN LOWER RECTUM	RESECTION; AGANGLIA FROM LOWER RECTUM TO ANUS
9. EG	8 YRS	M	NARROWING IN LOWER RECTUM	NARROWING PROVED AT SURGERY; RESECTION
10. FS	7 YRS	F	NARROWING IN LOWER RECTUM	NARROWING PROVED AT SURGERY; RESECTION

Figure 19

CASE	AGE	SEX	POENTGENOGRAPHIC FINDINGS	PATHOLOGIC FINDINGS
11. RT	10 DAS	M	NARROWING OF SIGMOID AND LOWER RECTUM WITH NORMAL APPEARING UPPER RECTUM	AUTOPSY; AGANGLIA IN SIGMOID AND LOWER RECTUM; NORMAL GANGLIA IN UPPER RECTUM
12. TB	1 MO	M	CHANGE IN CALIBRE OF COLON AT THE SPLENIC FLEXURE	AUTOPSY; AGANGLIA FROM SPLENIC FLEXURE TO ANUS
13. DM	5 WKS	F	NO BARIUM ENEMA	AUTOPSY; AGANGLIA FROM RECTO-SIGMOID TO ANUS
14. RD	5 MOS	M	RECTO-SIGMOID NARROWING	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS
15. KG	3 DAS	F	NO BARIUM ENEMA PRIOR TO SURGERY	DILATATION OF PROXIMAL COLON PROVED AT SURGERY; CECOSTOMY PERFORMED; BIOPSIES SHOWED AGANGLIA FROM HEPATIC FLEXURE DISTALLY
16. JH	2 YRS	M	RECTO-SIGMOID NARROWING	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS
17. JR	7 WKS	M	RECTO-SIGMOID NARROWING	NARROWING PROVED AT SURGERY; COLOSTOMY PERFORMED
18. DF	6 WKS	M	RECTO-SIGMOID NARROWING	SIGMOIDOSTOMY; RESECTION 3 YRS LATER AGANGLIA FROM RECTO-SIGMOID TO ANUS

Figure 20

CASE	AGE	SEX	ROENTGENOGRAPHIC FINDINGS	PATHOLOGIC FINDINGS
19. NB	3 WKS	F	ENTIRE COLON SMALL IN CALIBRE (MICRO-COLON)	AUTOPSY, AGANGLIA OF ENTIRE COLON, APPENDIX PERFORATED
20. GG	2 YRS	F	NARROWING OF SIGMOID	RESECTION, AGANGLIA FROM SIGMOID TO ANUS
21. KL	11 MOS	F	NARROWING OF SIGMOID	RESECTION, AGANGLIA FROM SIGMOID TO ANUS
22. PH	9 YRS	M	NARROWING FROM MID-SIGMOID TO ANUS	INTERNAL SPHINCTER BIOPSY. NO GANGLION CELLS; CONSERVATIVE THERAPY
23. WB	13 MOS	M	NARROWING FROM MID-SIGMOID TO ANUS	RESECTION, AGANGLIA FROM MID-SIGMOID TO ANUS
24. EM	9 MOS	F	NARROWING FROM RECTO-SIGMOID TO ANUS	NARROWING PROVED AT SURGERY, COLOSTOMY PERFORMED
25. GW	13 DAS	M	NARROWING OF ENTIRE COLON (MICRO-COLON)	SURGERY: PERFORATION OF LOWER ILEUM; COLOSTOMY; LATER ILEOSTOMY; AUTOPSY: AGANGLIA FROM SITE OF ILEAL PERFORATION TO ANUS
26. DS	2 YRS	M	NARROWING FROM RECTO-SIGMOID TO ANUS	NARROWED SEGMENT TO BE RESECTED

Figure 21

CASE	AGE	SEX	ROENTGENOGRAPHIC FINDINGS	PATHOLOGIC FINDINGS
27. JJ	7 YRS	M	NARROWING OF LOWER HALF OF RECTUM	CONSERVATIVE THERAPY, SURGERY PENDING
28. SB	3 YRS	M	NARROWING FROM RECTO-SIGMOID TO ANUS	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS
29. RH	1 MO	M	NARROWING OF ENTIRE RECTUM	RESECTION, AGANGLIA OF ENTIRE RECTUM
30. MT	1 MO	M	NARROWING FROM RECTO-SIGMOID TO ANUS	NARROWING PROVED AT SURGERY; COLOSTOMY PERFORMED
31. JM	7 YRS	F	NARROWING OF ENTIRE RECTUM	CONSERVATIVE THERAPY; SURGERY PENDING
32. IG	8 MOS	F	NARROWING IN LOWER RECTUM	CONSERVATIVE THERAPY; SURGERY PENDING
33. GD	16 MOS	M	NARROWING OF SIGMOID	RESECTION; AGANGLIA FROM SIGMOID TO ANUS
34. RG	8 MOS	M	ANNULAR NARROWING IN PROXIMAL SIGMOID	RESECTION; AGANGLIA FROM PROXIMAL SIGMOID TO ANUS
35. BK	10 YRS	F	NARROWING OF RECTO-SIGMOID	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS
36. PD	15 MOS	F	NARROWING OF SIGMOID	RESECTION OF NARROWED SIGMOID; AGANGLIA OF RESECTED SEGMENT

Figure 22

CASE	AGE	SEX	ROENTGENOGRAPHIC FINDINGS	PATHOLOGIC FINDINGS
37. HD	2 MOS	M	NARROWING OF ENTIRE RECTUM	RESECTION; AGANGLIA OF ENTIRE RECTUM
38. JG	4 YRS	M	NARROWING OF SIGMOID	RESECTION; AGANGLIA FROM SIGMOID TO ANUS; IVP SHOWED LEFT MEGALO-URETER
39. JL	2 YRS	M	NARROWING OF LOWER HALF OF RECTUM	RESECTION OF SIGMOID; TWO YEARS LATER AGANGLIONIC LOWER RECTUM RESECTED
40. EH	4 YRS	M	NARROWING FROM PROXIMAL SIGMOID TO ANUS	RESECTION; AGANGLIA FROM PROXIMAL SIGMOID TO ANUS
41. RW	6 MOS	M	NARROWING FROM SPLENIC FLEXURE TO ANUS	RESECTION; AGANGLIA FROM SPLENIC FLEXURE TO ANUS; DIED POST-OPERATIVELY.
42. ES	4 DAS	F	NARROWING FROM SPLENIC FLEXURE TO ANUS	RESECTION; AGANGLIA FROM SPLENIC FLEXURE TO ANUS; DIED POST-OPERATIVELY
43. CS	3 YRS	M	NARROWING FROM SPLENIC FLEXURE TO ANUS	RESECTION; AGANGLIA FROM SPLENIC FLEXURE TO ANUS; DIED POST-OPERATIVELY
44. LS	6 MOS	F	NARROWING FROM RECTO-SIGMOID TO ANUS	RESECTION; AGANGLIA FROM RECTO-SIGMOID TO ANUS

Figure 23

News and Comment

ANNOUNCEMENTS

Refresher Course in Pediatric Neurology.—This year's refresher course for qualified pediatricians at Tulane, entitled "Pediatric Neurology," Feb. 27 through March 3, 1956, will have as its guest speaker Dr. Douglas Buchanan, of the University of Chicago. A comprehensive program will deal with basic considerations and clinical management of convulsive disorders, degenerative diseases of the nervous system, infections of the brain and meninges, and other such broad subjects. Selected members of the entire medical school faculty will participate, and stress will be placed mainly on clinical aspects of neurologic disorders of early life. Those interested should apply to Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12. Registration, as usual, is limited to 40 qualified specialists.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

FURTHER EXPERIMENTS ON THE UTILIZATION OF CALCIUM FROM SALTS BY COLLEGE WOMEN. MARY BROWN PATTON, J. Nutrition **55**:519 (March 10) 1955.

Mary Brown Patton used nine college women for her experiments, and statistical analysis of the data showed that under present experimental conditions, milk, calcium gluconate, and calcium carbonate were utilized equally well by these subjects as a source of calcium. Basal metabolic rate was inversely related to calcium utilization—the greater the rate the less the retention.

FREDEEN, Kansas City, Mo.

CELIAC DISEASE: WHAT IS IT? L. EMMETT HOLT JR., J. Pediat. **46**:369 (April) 1955.

Celiac disease is a poorly understood chronic functional disorder of intestinal assimilation. It is a vague term applied to children with poor muscle tone and little subcutaneous fat—cranky children with pale and frothy stools.

There is a lot of confusion about what "celiac disease" is. Some make the diagnosis with the help of response to a "celiac diet." But there are a number of "celiac diets," some of them contradictory. All celiac diets appear to have produced excellent results, not surprizing in a condition with a tendency to spontaneous improvement, even though it be slow and punctuated by relapses.

How about laboratory tests? Is increased fat in the stool a sign of celiac disease? No, says Holt, we have no simple clinical method for measuring fat absorption. Percentage of fat in the stool is not a reliable measure of absorption. As for starch, there is no valid evidence that undigested starch in the stool represents mild or early celiac disease with specific therapeutic indications.

Holt suggests that intolerance to fat and carbohydrate may not be induced by the food but by some exogenous factor, such as infection in cases of acute diarrhea. Increased fat in the celiac diet increases the fat loss in the stool but also increases fat absorption. He is against the therapy of avoidance.

Although polysaccharide itself appears safe to give, wheat gluten may initiate relapse in celiac disease. This problem of food sensitivity needs to be studied carefully in every case and only those starchy foods excluded in which sensitivity has been clearly demonstrated. We do not need to exclude either fats or sugars from the diet. Since intercurrent infections are responsible for most relapses, prophylactic and therapeutic antibiotics are indicated.

MACDONALD, Pittsburgh.

COMPARISON OF NUTRITIONAL RESULTS WITH EVAPORATED MILK AND POOLED MOTHER'S MILK IN YOUNG INFANTS. A. SINIOS, Ztschr. Kinderh. **75**:634, 1955.

Fifty premature infants and infants in the first trimester were fed evaporated homogenized milk without addition of a second carbohydrate, and 49 infants of the same age received pooled mother's milk.

The results as measured by weight gain and incidence of gastrointestinal disturbances showed no statistically significant difference between the two groups.

GLASER, Baltimore.

ACTION OF DIHYDROERGOTAMINE UPON GLUCOSE METABOLISM IN DYSTROPHY. K. B. CHOREMIS and C. WONTA, Ztschr. Kinderh. **75**:694, 1955.

The antagonistic action of ergotamine against epinephrine with regard to blood sugar levels was tested in eutrophic and dystrophic infants. In eutrophic infants a moderate hypoglycemia was produced, in dystrophic infants the blood sugar level was lowered even further.

This was explained by the glycopenia of the dystrophic infants in presence of their almost normal blood sugar level which is caused by hyperadrenalemia, and led to the conclusion that the blood sugar level is dependent not only upon exogenous sugar intake but also upon endocrine regulation.

GLASER, Baltimore.

Prematurity and Congenital Deformities

ANENCEPHALY IN TWINS. DU-KAN LIN and H. P. PLENK, Am. J. Roentgenol. **73**:219 (Feb.) 1955.

The average incidence of anencephaly in human births is approximately 0.7 per 1000 births. The authors have been able to find nine cases of anencephaly in twin births which have previously been reported in the medical literature. In seven of these nine cases only one of the twins was anencephalic, while both twins were anencephalic in two cases. They report a case of their own in which both female twins were anencephalic, and the diagnosis was made by means of a routine roentgenogram of the abdomen which had been taken four weeks before delivery. The incidence of congenital anomalies of all types is higher in the offspring of parents who have already produced one or more offspring with a congenital anomaly than it is in the offspring of the general population. The presence of anencephaly in both identical twins has led some authors to the conclusion that the condition is inherited, rather than caused by an intrauterine accident. The ratio of three females to one male anencephalic also suggests a hereditary factor, perhaps linked with the sex chromosome. However, anencephaly, spina bifida, and other anomalies of the central nervous system have been produced in animals by attacking the developing fetus with concentrated salt solutions and ultraviolet rays. The authors emphasize the ease with which the diagnosis of anencephaly can be made ante partum by means of roentgenography of the maternal abdomen.

WEILAND, Grove City, Pa. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

RECENT ADVANCES IN RETROLENTAL FIBROPLASIA. MARGARET HENRY, California Med. **81**:272 (Oct.) 1954.

Retrolental fibroplasia is the commonest cause of preschool blindness. Changes identical to retrolental fibroplasia in humans have been produced in animals by exposing them to high oxygen concentration.

Oxygen should be ordered for premature infants in a careful and precise manner. Concentrations of over 40% should be avoided whenever possible. Withdrawal to air should be a gradual process.

PRYOR, Redwood City, Calif.

POST-OPERATIVE VELO-PHARYNGEAL MOVEMENTS IN CLEFT PALATE CASES. MCKENZIE BUCK, J. Speech & Hearing Disorders **19**:288-294 (Sept.) 1954.

X-ray studies of 20 postoperative unilateral cleft palates showed marked differences in velar activity between cleft palate and normal subjects. The velopharyngeal opening during phonation of vowels was significantly greater in the cleft-palate group. The anterior movement of the posterior pharyngeal wall was similar for both groups. Some of the cleft-palate subjects approximated a velopharyngeal closure against adenoidal tissue. The cleft-palate subjects used more vertical movements of the velum. Nasality in cleft-palate patients is mainly related to the effectiveness of the velopharyngeal closure.

PALMER, Wichita, Kan.

ESOPHAGEAL HIATAL DIAPHRAGMATIC HERNIA. S. W. HARRINGTON, Surg., Gynec. & Obst. **100**:277 (March) 1955.

This report summarizes the author's experience with 489 operations on different types of hiatal hernias. The classification which he employs is as follows: (1) paraesophageal hiatal hernia, (2) hiatal hernia with elevation and displacement of the esophagus, and (3) hiatal hernia caused by a short esophagus.

In the paraesophageal type of hiatal hernia, comprising roughly 15% of the entire series, the esophagus is of normal length and is not elevated above the diaphragm. The stomach and possibly other abdominal viscera may herniate alongside of the esophagus into the posterior mediastinum and into either or both sides of the thoracic cavity. This type is most satisfactorily treated by surgery.

In the second type of hiatal hernia the esophagus is of normal length but its lower end is displaced and does not extend to the diaphragm. The stomach usually herniates into the posterior mediastinum or thoracic cavity. This form of hernia is the commonest, making up about 67% of the total series, and in this group fall most of the surgical failures and postoperative recurrences.

When the hiatal hernia is associated with a short esophagus, the latter may be of the congenital type (5%) or acquired type (13%). In the latter group the contractures resulting from ulceration and fibrosis are responsible for structural changes which draw the cardia of the stomach above the diaphragm. This condition is often associated with stenosis of the lower part of the esophagus.

The author feels that most esophageal hiatal hernias are basically congenital in origin.

Roentgenographic examination is most important in establishing the diagnosis, while esophagoscopy is essential for the determination of such associated conditions as esophagitis, peptic ulceration from reflux of gastric secretions, traumatic ulceration at the cardia, and strictures, as well as spasm of the esophagus. Esophagoscopy must be regarded as a routine part of the general evaluation because the finding of lesions complicating the hernia, as well as lesions not related to the hernia, will often alter the method of management as well as the type of treatment required.

It is interesting to note that in the 489 cases in which hiatal hernia operations were performed approximately 3 previous erroneous clinical diagnoses were made per case before the correct diagnosis was established. In order of frequency these erroneous diagnoses were cholecystitis, cholelithiasis, gastric ulcer, duodenal ulcer, hyperacidity, secondary anemia, cardiac disease, carcinoma of the cardia, stricture of the esophagus, intestinal obstruction, appendicitis, and thoracic tumor.

The surgical techniques employed are illustrated, and the results of treatment are presented. It is concluded that only those patients whose symptoms are definitely related to the hernia and who do not respond to conservative measures should be treated surgically.

FRIEDBERG, Chicago [A. M. A. ARCH. OTOLARYNG.].

A REPORT OF SEVEN CASES OF CHONDRO-OSTEO-DYSTROPHY (MORQUIO'S DISEASE). W. F. TOWNSEND-COLES, Arch. Dis. Childhood **29**:7 (Feb.) 1954.

Seven cases of chondro-osteo-dystrophy occurring in three sets of siblings in northern Sudanese families are described. In each set the parents were close blood relatives. One father had simultaneously produced a large family of healthy children by a second wife to whom he was not a blood relation.

KELLY, Milwaukee.

PRENATAL HAZARDS AND PEDIATRICS. J. M. SALA PONSATI, Arch. pediat., Barcelona, **4**:349-357 (Jan.-Feb.) 1954.

The author cites the statistics in various countries, which show a steady fall in the infant mortality rate and the perils to life in obstetrical practices in some areas in Spain. He also feels that factors other than medical play a big part in the neonatal deaths. Among these are social and economic conditions, especially malnutrition.

He gives some thought to the age and marital status of the mother and the number of deliveries experienced by the mother.

The newer knowledge of toxins, etc. which may pass the placental barrier has helped clarify certain congenital anomalies. He calculates that while infant mortality rates have fallen in private practice, at least 20,000 infants die yearly in Spain from causes which could have been prevented.

ALLEN, Santa Fe, N. M.

A CASE OF CONGENITAL HEMIHYPERTROPHY OF THE FACE. D. MOFFI, Maandschr. kindergeneesk. **22**:330 (Oct.) 1954.

The author describes a case of congenital hemihypertrophy of the face in combination with epilepsy. On the hypertrophic side the cerebral hemisphere and ventricle were also enlarged.

FROM THE AUTHOR'S SUMMARY.

PROGERIA. SANTIAGO MUZXO and OSCAR ALONSO, Rev. chilena pediat. **25**:325 (July) 1954.

A typical case of progeria is shown in which, apart from the classical symptoms described, the cranial x-ray showed calcifications of the choroid plexus.

FROM THE AUTHOR'S SUMMARY.

Newborn

LONGITUDINAL STUDY OF THE INCIDENCE OF CENTRAL NERVOUS SYSTEM DAMAGE FOLLOWING ERYTHROBLASTOSIS FETALIS. MARGARET H. JONES, RUSSELL DANS, CAROL B. HYMAN, PHILLIP STURGEON, and FREMONT P. KOCH, Pediatrics **14**:346 (Oct.) 1954.

One hundred unselected cases of erythroblastosis fetalis treated at Children's Hospital in the newborn period have been followed from six months to five years in an effort to evaluate the relation of central-nervous-system signs in the newborn period to neuromuscular handicap and over-all development later.

Of those showing no central-nervous-system signs in the newborn period, 4% showed definite abnormality later.

Of those showing equivocal signs in the newborn period, 33% showed definite abnormality later.

Of those having definite signs early, 100% continued to show abnormality in infancy and childhood.

There was no relation of the severity of the signs in the newborn period to the severity of the later handicap.

It is suggested, therefore, that one cannot be certain of the later normality of an infant showing no definite or equivocal central-nervous-system involvement in the newborn period. Careful following of all erythroblastotic infants until 6 to 8 years of age or longer is advisable.

FROM THE AUTHORS' SUMMARY.

THROMBOCYTOPENIC PURPURA IN THE NEWBORN. M. BRENDA MORRIS, Arch. Dis. Childhood **29**:75 (Feb.) 1954.

Three further cases of thrombocytopenic purpura in the newborn are described. In one of these the mother had a symptomless thrombocytopenia which was discovered on the day after delivery and which lasted less than a week. The literature is briefly reviewed, and it is concluded that thrombocytopenia of the newborn is a self-limiting condition distinct from chronic idiopathic thrombocytopenic purpura.

KELLY, Milwaukee.

THE TRANSITORY ABSENCE OF SEVERAL CLOTTING FACTORS IN A NEWBORN BABY. S. VAN CREVELD and I. A. MOCHTAR, Arch. Dis. Childhood **29**:290 (Aug.) 1954.

An infant is described with congenital heart disease and heart failure and slight symptoms of a hemorrhagic diathesis. All the clotting factors taking part in the second phase of the clotting process were temporarily absent or considerably decreased.

Special stress is laid on the fact that at the beginning of life the plasma contained practically no fibrinogen but notwithstanding exerted a normal coagulation-promoting actively upon hemophilic blood. The so-called thromboplastin-generation test gave a normal result, although the plasma contained practically no proconvertin.

KELLY, Milwaukee.

CONGENITAL DEAFNESS AND HAEMOLYTIC DISEASE OF THE NEWBORN. L. FISCH and D. A. OSBORN, Arch. Dis. Childhood **29**:309 (Aug.) 1954.

In an investigation of 891 children with congenital preceptive deafness, evidence of hemolytic disease of the newborn was found in 27, of whom 20 had varying degrees of choreoathetosis. There appeared to be some correlation between the degree of deafness and the severity of other neurological signs.

These cases were compared with other cases of congenital perceptive deafness associated with anoxia and birth injury (83), prematurity (68), heredity (50), and maternal rubella (69). A similarity was noted between the audiograms of the cases associated with hemolytic disease and anoxia, respectively, in both of which there was selective high-frequency loss. It is suggested that in these two groups there is at least a common site of the lesion if not a common etiology.

KELLY, Milwaukee.

UNILATERAL DIAPHRAGMATIC PARALYSIS AND ERB'S PALSY IN THE NEWBORN. N. E. FRANCE, Arch. Dis. Childhood **29**:357 (Aug.) 1954.

Intermittent rapid breathing in a 16-day-old infant with Erb's palsy led to the radiological diagnosis of right diaphragmatic paralysis. During the remaining 31 days of life, respiratory distress increased and evidence of pulmonary collapse appeared.

At necropsy avulsion of the anterior roots of the cervical nerves supplying the right phrenic nerve was found. Adrenal calcification following old hemorrhage was also present.

Previously described necropsy records are reviewed.

KELLY, Milwaukee.

SETTING SUN REFLEX IN THE NEWBORN. H. STILLHART, Helvet. paediat. acta **9**:298 (Oct.) 1954.

The author reports 121 cases presenting the so-called setting-sun reflex-like phenomenon (s. s. p.) observed from 1946-1953 in the "Kant. Säuglingsheim Zurich" which were systematically followed up.

The most important results are as follows:

1. The s. s. p. is most often observed during the first five weeks of life. In premature infants it can be observed for as long as three months. Only in cases of brain damage does it exist beyond the third month. It appears spontaneously or when one changes the infant position.

2. The s. s. p. is often associated with cerebral lesions, especially "kernicterus" and those damages with increased intracranial pressure. In icterus gravis it is always present or producible as an early sign of kernicterus. When this sign outlasts the period after birth one must consider that the nuclei are damaged. When the s. s. p. lasts more than three months or is very intense for at least four weeks, our experience shows that one has to deal with a serious case of cerebral damage.

3. In prematures the s. s. p. is current and has no clinical significance of prognostic value.

4. From time to time the s. s. p. can be observed in full-term babies without any accompanying cerebral damage. In such cases it lasts no more than a few days, exceptionally a few weeks. Its clinical significance is unknown.

5. The author also reports a case showing a relation between the s. s. p. and a defect in the midbrain.

FROM THE AUTHOR'S SUMMARY.

VULVOPERINEAL LESIONS IN THE NEWBORN. DELIO AGUILAR GIRALDES and JORGE GALARRAGA, Recien nacido **2**:77 (March) 1954.

The authors report two cases of vulvoperineal lesions resulting from intrapartum trauma in breech presentations. They were the result of incompetent and rough procedures.

In the first case, of deeper and more complete laceration, they adopted expectant therapy (antibiotics and local medication), and the other was sutured in addition to the same treatment.

The sequence and evolution of the lesions was the reason of the difference in both treatments. The two girls had favorable results.

A commentary about the moral, social, and legal consequences is added.

FROM THE AUTHORS' SUMMARY.

PERITONITIS IN THE NEWBORN. HUMBERTO GARCES, FELIPE FERNANDEZ, and ALBERTO GUZMAN, Rev. chilena pediat. **25**:312 (July) 1954.

The experience with fibropurulent peritonitis in the newborn infant obtained in the "Roberto del Rio" Hospital is reported. In a period of 15 years 44 cases are gathered.

The most important causes of this condition were sepsis (27.2%), omphalitis (20.4%), enterocolitis (18.1%), and congenital malformations of the gastrointestinal tract (15.9%).

The general clinical symptoms are the same as those of a serious sepsis, with the added fact of the intensity and frequency of vomitings. The most deeply local signs are enlargement of the abdomen with superficial vein circulation, eversion of the naval, and edema of the abdominal wall. Abdominal pain is difficult to fix at this age.

Postmortem examination showed in 47.7% of the cases free fibrinopurulent exudate in the peritoneal cavity, in 45.4% a located fibrinopurulent peritonitis, and in 6.8% of the cases only fibrinous exudate.

It is pointed out that clinical diagnosis is difficult, and the contribution of x-ray examination is discussed.

The evolution is brief, the average being 4.1 days after the apparent beginning of the disease. The prognosis is very serious, and there are only very few cases of recovery reported.

The treatment is medical-surgical, and it is designed to attack the etiological bacteria, to drain off the pus, to correct the primitive condition that has produced the peritoneal infection.

FROM THE AUTHORS' SUMMARY.

Acute Contagious Diseases

POSTVACCINAL MENINGOENCEPHALITIS. FERRUCCIO CORRIAS, Ann. ital. pediat. **7**:401 (Oct.) 1954.

A meningoencephalitic symptomatology was seen after 14 days in a patient vaccinated against smallpox. After discussing the diagnosis, the author sums up the present knowledge we have now on the pathologenetic interpretation of postvaccinic encephalitis.

FROM THE AUTHOR'S SUMMARY.

AN EPIDEMIC OF POLIOMYELITIS TRACEABLE TO DOMESTIC ANIMALS (CATS). N. COREA-MANNO, Pediatria **62**:568 (July) 1954.

An epidemic of poliomyelitis involving seven children 5 to 16 months of age and living on the outskirts of a small village seemed to be traceable to cats. Two cats living in two of the homes had died of an acute illness shortly before the children became sick. All the cases occcurred over a period of one month. No other cases occurred nearby.

HIGGINS, Boston.

MODERN TREATMENT OF SCARLET FEVER AND ANTISTREPTOLYSIN REACTION. KLAUS SEELEMANN and HILDEGARD NEUMANN, Deutsche med. Wchnschr. **79**:1825 (Dec. 3) 1954.

The titer of the antistreptolysin reaction of the serum of children with scarlet fever increased rapidly when no treatment was given. When they were treated with penicillin, this increase was suppressed. Delayed treatment with penicillin, addition of Omnadin as Omnacillin, and simultaneous anti-scarlet-fever vaccination did not inhibit this inhibition. (Omnadin is a preparation containing bacterial protein, fat, and lipids.) The antistreptolysin reaction is an important indicator for a previous contact with hemolytic streptococci extending over a period longer than one week.

Antistreptolysin represents only a partial factor of the total immunity against scarlet fever, but the production of this partial factor is suppressed by treatment with penicillin. It is to be noted that in a certain number of untreated scarlet fever patients the increase of the antistreptolysin titer does not occur. Scarlet fever vaccine does not contain an antigen stimulating the production of antistreptolysin in man.

AMBERG, Rochester, Minn.

THE TREATMENT OF SCARLET FEVER WITH ONE OR TWO INJECTIONS OF DEPOT PENICILLIN IN OIL. JOACHIM STOERMER, Monatsschr. Kinderh. **102**:291-295 (June) 1954.

One hundred children with scarlet fever were treated with intramuscular administration of procaine penicillin in oil. Patients weighing up to 15 kg. (up to about 4 years of age) received one injection of 1,000,000 units, patients weighing between 15 and 25 kg. (4-8 years of age) 1,200,000 units, and those weighing more than 25 kg. (older than 8 years) received two injections, namely, 1,500,000 units for the first dose and 900,000 units on the fourth day. Therapy was begun on the fourth day of the illness except in severely ill patients. Strict isolation precautions were enforced.

One patient in the series developed rheumatoid arthritis. There was one relapse of severe sore throat with negative throat culture on the eighth day of illness. One patient developed fever of 39.7 C (103.5 F) on the fifth day of illness without other abnormal clinical findings and with negative throat culture. One patient experienced recurrence of scarlet fever four and one-half weeks after onset of the first illness. A sibling of this patient developed scarlet fever a few days later. All patients in this study were hospitalized for 7-10 days.

HARTENSTEIN, Milwaukee.

DIASTASE DETERMINATIONS IN THE DIFFERENTIAL DIAGNOSIS OF MUMPS MENINGOENCEPHALITIS. R. BIELING and F. KOCH, Monatsschr. Kinderh. **102**:375-379 (Aug.) 1954.

In a group of 12 children with such conditions as tuberculosis, scarlet fever, other infections, and Mongolism no blood diastase values above 32 Wolgemuth units (WU) and no urine diastase

values above 64 WU were found. According to this method (Wolgemuth) blood diastase values above 128 units and urine values above 256 units are considered abnormal.

In a group of 10 children with mumps without complications such as meningoencephalitis maximum diastase value for blood were 1024 WU and 4096 WU for urine.

Of 15 children with mumps complicated by meningoencephalitis and 2 with meningoencephalitis without clinical evidence of parotid involvement blood diastase values ranged between 64 and 512 WU, urine values between 512 and 1024 WU. Mumps complement fixation tests were performed in 11 of these 17 patients and were found to be positive in all cases.

Of 17 children with other infectious diseases of the central nervous system, such as encephalitis, poliomyelitis, Guillain-Barré syndrome, and measles encephalitis, blood and urine diastase values ranged between 8 and 64 WU. Complement fixation tests were performed in 11 of these patients and were negative in all of them.

The authors believe that elevated blood and urine diastase levels are valuable in establishing an early diagnosis of mumps meningoencephalitis in the differential diagnosis of the various nonbacterial central-nervous-system infections. Especially so since mumps complement fixation titers usually become positive later in the course of the disease than the diastase values.

HARTENSTEIN, Milwaukee.

Acute Infectious Diseases

SIMPLICITY IN THE TREATMENT OF MENINGITIS. ARCHIBALD L. HOYNE, Ann. Int. Med. **41**:1164, 1954.

Hoyne reviews the therapy of meningitis from a historical standpoint and advocates the use of simple measures in the management of all cases of meningitis. He believes that a lumbar puncture should be reserved for diagnostic purposes only; more than one lumbar puncture is unnecessary in cases of purulent meningitis. However, if there is difficulty in isolating the organism or in establishing a diagnosis, more than one lumbar puncture is justified. If the patient has a positive blood culture or petechiae in the skin, lumbar puncture is not necessary. Repeated lumbar punctures are unnecessary in following a patient's clinical course.

In regard to intrathecal medication, the author feels that the estimated spinal level is about 50% to 75% of the blood level. Therefore medication can be administered orally, intramuscularly, or intravenously for satisfactory spinal fluid concentrations.

By using these principles as a basis, several thousand patients were successfully treated in the Cook County Contagious Disease Hospital. The fatality rate was 10% in cases of Meningococcus meningitis, 16% in Hemophilus influenzae meningitis, and 45% in tuberculous meningitis. None of the patients with tuberculous meningitis received intrathecal medication.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE PATHOLOGIC ASPECTS OF ASCARIASIS. MCKENZIE P. MOORE JR., South. M. J. **47**:825 (Sept.) 1954.

The life history of Ascaris lumbricoides is briefly described. There are three autopsy reports of children who died from an infestation with this worm. These reports illustrate various complications of ascariasis, such as dilatation of the heart, esophageal perforation with viable worms in the pleural cavity, partial intestinal obstruction by worm masses, pancreatic duct obstruction by worms with secondary hemorrhagic necrosis of the pancreas, and perforation of the stomach with peritonitis and viable worms in the peritoneal cavity. Three cases reported are given, only one of which concerns a child. These patients all recovered. In one a localized granulomatous lung lesion was surgically removed, in another the appendix partially filled with Ascaris was surgically removed, and in the other a partial intestinal obstruction occurred necessitating surgical exploration. There are seven illustrations, each one pertaining to one of the case or autopsy reports.

LOGAN, Rochester, Minn.

PHLEBOTOMUS FLY. R. ZARIGUIEY ALVAREZ, Arch. pediat., Barcelona **3**:441-457 (Jan.-Feb.) 1953.

The Phlebotomous fly is believed by most investigators to be the insect vector of kala-azar. Kala-azar is very prevalent in many areas of Spain, and a full description of this fly is given.

There are five species in Spain. Many illustrations showing anatomical details in the male and female of each species, their life cycles, and distribution are also shown.

Methods of capturing the insects, preparing them to be sent for identification, etc., are also given. The species described are Phlebotomus papatasii, P. perniciosus, P. ariasi, P. sergenti, and P. minutus.

The author urges assistance in helping to correlate the number of flies present in any community with new cases of kala-azar in order to plan better for prophylaxis.

ALLEN, Santa Fe, N. Mex.

THE THREE-DAY FEVER-EXANTHEMA OF SMALL CHILDREN: EXANTHEMA SUBITUM. A. WINDORFER, Deutsche med. Wchnschr. **79**:1201 (Aug. 13) 1954.

Exanthema subitum, rarely seen after the second year of life, is discussed on the basis of 117 cases in four years. It is emphasized that in some instances the disease may be quite severe. In 35 cases convulsions occurred in the febrile phase, with other symptoms suggesting a participation of meninges and brain in the disease process. The author feels that a fatal outcome is not excluded entirely.

AMBERG, Rochester, Minn.

THE ETIOLOGY OF THE ABSCESS-FORMING RETICULOCYTIC LYMPHADENITIS, A DISEASE OF PRACTICAL IMPORTANCE, OFTEN SIMULATING ACUTE APPENDICITIS. W. KNAPP and W. MABHOFF, Deutsche med. Wchnschr. **79**:1266 (Aug. 27) 1954.

From mesenteric lymph nodes obtained on surgery for supposed appendicitis in three cases, 10½, 11½, and 17 years of age, it was possible to grow Pasteurella pseudotuberculosis. With material from the lymph nodes as well as with pure culture injected intraperitoneally, a lesion similar to those of the patients could be produced in animals. The serum of one of the patients agglutinated the micro-organisms from the three, but not P. multocida and P. tularensis. In 12 cases agglutination tests only could be performed, besides the histological examination. The age varied from 10 to 24½ years; the titer varied from 1 : 200 to 1 : 5120. All observed cases were benign.

AMBERG, Rochester, Minn.

INFLUENZA INFLAMMATION IN CHILDREN IN A COUNTRY HOSPITAL. J. ZELENKA, M. ERHARTOVA, and H. PIKARTOVA, Pediat. listy **9**:263, 1954.

The authors describe a clinical test of 23 pneumonia cases in sucklings and 13 cases in older children with influenza etiology.

FROM THE AUTHORS' SUMMARY.

TETANUS NEONATORUM. G. VAN HAESEBROUCK, Maandschr. kindergeneesk. **22**:415 (Dec.) 1954.

The author gives observations of one case of tetanus neonatorum. The incubation period was of four days, and there was recovery. The introduction of chlorpromazine (Largactil—Specia, Paris) in the treatment of tetanus neonatorum appears to be of great importance.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

TUBERCULOSIS MENINGITIS AND ITS MANAGEMENT. H. L. BASU, Indian J. Pediat. **21**:161-166 (July) 1954.

Thirty-one cases of tuberculous meningitis in 1952 and 1953 and two months of 1954 were analyzed. Treatment consisted of streptomycin, isoniazid, and paraaminosalicylic acid (PAS). In 1952 nine cases were treated with streptomycin intramuscularly and intrathecally and PAS orally. One case died, three went home with very little improvement after three weeks' treatment, and five cases improved and were discharged after three or four months.

In 1953 and 1954 twenty-two cases were treated in the same way plus the use of hydrazide intramuscularly. In this group there were two death. Seventeen cases were improved and discharged after three to five months.

McGUIGAN, Evanston, Ill.

AN ATTEMPT AT PREVENTING MENINGEAL ADHESIONS IN TUBERCULOUS MENINGITIS WITH THE USE OF DI-ARGENTIC SULFONE. J. GRENIER, J. BAVAY, A. ROBERTI, and G. KAHAN-LEMAIRE, Presse méd., Supp. 68, p. 1406, Oct. 16, 1954.

In some cases of tuberculous meningitis the failure of the antibiotic treatment may be due not to the resistance of the bacilli to the drug but to the meningeal blocking. It is therefore likely that by avoiding the development of meningeal adhesions and using at first such an antibiotic as possesses particularly penetrating properties one might obtain still more satisfactory results and improve the percentage of recoveries.

To this purpose the authors attempted to combine silver sulfone with the usual antibiotics in order to prevent the formation of meningeal adhesions or to remove these if they have already developed. Although they did not consider that silver sulfone brings any further toxic factor to the common therapy of tuberculous meningitis, they took care to check the blood picture and the urine contents. In their view, at least one of the six cases here reported has been certainly cured by the effect of this combination, as demonstrated by the spectacular progressive clearance of the adhesions due to a severe chronic arachnoiditis. The cerebrospinal fluid pressure, which was null at onset, was shown to be quite normal four months later.

FROM THE AUTHORS' SUMMARY.

INFLUENCE OF INFECTIOUS DISEASE OF CHILDHOOD ON THE EVOLUTION OF GLANDULAR-PULMONARY TUBERCULOUS PROCESSES. GIUS ALFONSO. Ann. ital. pediat. **7**:331 (Oct.) 1954.

The author has studied the influence exercised by the occurrence of some acute infectious diseases (measles, chicken pox, scarlet fever, whooping cough, mumps) on the course of primary tuberculosis.

In 300 children he found clinical or clinicoradiological aggravations of 64% in measles, of 14% in scarlet fever, of 7.5% in chicken pox, of 45% in whooping cough, and no aggravation in mumps.

He discusses the differential criteria for distinguishing real tuberculous aggravation from pulmonary localization from virus or from germs responsible for the acute affection.

As for the mechanism of action, he discusses (1) the mechanical theory (passage of bacillus from involved glands into other parts); (2) the immunobiologic theory (conceived as a lowering of the defenses); (3) the possibility of an action of parallergic type by substances active by the agent of the acute diseases in a location especially sensitized by the tubercular disease.

FROM THE AUTHOR'S SUMMARY.

THE INCIDENCE OF KOCH'S BACILLI OF VARIOUS DEGREES OF STREPTOMYCIN RESISTANCE IN CASES OF TUBERCULOUS MENINGITIS IN CHILDREN AND ADULTS: THE NECESSITY TO ADAPT TREATMENT ACCORDINGLY. A. DEGLI ESPOSTI, Clin. pediat. **36**:677 (Sept.) 1954.

Although in the five and one-half years previous to October, 1952, only 0.7% of the patients with tuberculous meningitis had streptomycin-resistant tubercle bacilli in their spinal fluids, the percentage had risen to 37.5% in the year October, 1952, to October, 1953. Isoniazid therapy had to be given a more important place in the treatment of those cases where the meningitis was caused by streptomycin-resistant organisms.

Only a few of these patients had previously had sustained treatment with antibiotics. However, the view is expressed that the frequent unnecessary use of antibiotics or of inadequate streptomycin therapy is the probable cause in the incidence of streptomycin resistance. These findings emphasize the necessity of increasing the number of newborn infants receiving vaccination against tuberculosis.

HIGGINS, Boston.

THE SIGNIFICANCE OF VELEZ'S INDEX AND OF ALLERGOMETRIC MEASUREMENTS IN EXUDATIVE-ALLERGIC TUBERCULOSIS. A. COLLETTA, Pediatria **62**:558 (July) 1954.

Velez's index is positive or negative according to whether the number of two-lobe neutrophilic blood cells is greater or less than the number of three-lobe cells. Allergometric measurements are made on the relative sizes of the skin reactions to different concentrations of tuberculin.

These tests furnish important data, which are of significance in determining the efficacy of treatment in cases of tuberculosis in children. Data from 20 cases are presented.

HIGGINS, Boston.

A Case of Tuberculous Meningitis Treated and Recovered in the Course of Lymphogranuloma Malignum. Paelo Prosperi and Angelo Ulivelli, Riv. clin. pediat. **54**:106 (Aug.) 1954.

The authors describe the case of a patient affected by mediastinal lymphogranuloma and tuberculous meningitis; these affections developed one after the other and apparently independantly.

During a period of improvement of the lymphogranuloma, treated with x-ray therapy, the 28-year-old woman fell ill with tuberculous meningitis. Responding to the now classic therapy, she recovered in about three months. Two months after the recovery confirmed by the cerebrospinal fluid findings, the patient presented hyperthermia and glandular tumefactions which by a biopsy showed the recurrence of lymphogranuloma.

The authors, after a rapid review of bibliographic, clinical, and experimental data, affirming or denying an analogy between lymphogranuloma and tuberculosis, conclude that no convincing data in support of this analogy seemed now to exist, and also do not in relation to the case described.

From the Authors' Summary.

Tuberculin Sensitivity in Cutaneous and Intradermal Tests. Pedro M. Gonzalez Outon, Rev. españ. pediat. **10**:41-43 (Jan.-Feb.) 1954.

The author compares the accuracy of various skin tests in tuberculosis as confirmed by x-ray information and concludes skin tests are just as accurate as the intradermal tests and much less dangerous to the infant.

Allen, Santa Fe, N. Mex.

Hemagglutination Tests in Children Who Had Received BCG. Hisashi Yoshida and Shozo Naito, Monatsschr. Kinderh. **102**:301-303 (June) 1954.

Using the Middlebrook-Dubos hemagglutination test in children who had received BCG, it was found that (1) Titers decreased three to seven months after vaccination and had increased as early as three weeks after BCG administration. There were isolated cases in which the hemagglutination tests were positive before appearance of positive tuberculin tests and after disappearance of positive tuberculin tests. (2) Increase in hemagglutination titers occurred more rapidly when BCG had been administered percutaneously than when administered intracutaneously. Decreases in titers, however, were concurrent with both methods. (3) Using the hemagglutination tests it was not possible to differentiate between children who had received BCG and those who had active tuberculosis.

Hartenstein, Milwaukee.

Extrapleural Pneumothorax in the Treatment of Tuberculosis in Children and Adolescents. K. Simon and R. Hoppe, Monatsschr. Kinderh. **102**:367-370 (Aug.) 1954.

In children and adolescents with active cavernous pulmonary tuberculosis extrapleural pneumothorax was performed 100 times. One patient died four days after the procedure. The cause of death was found to be contralateral basal pneumonia. Postoperative hemorrhage occurred in 16% of cases; in three instances it was considered severe. Blood transfusions were curative of the bleeding in all instances. In seven instances the procedure was deemed unsuccessful, as the tuberculous pulmonary lesions remained open. In 67% of patients, lesions were bilateral, and in this group collapse therapy had to be carried out on both sides in 15 instances.

In view of the fact that 92% of patients treated with extrapleural pneumothorax became sputum-negative and that mortality was only 1%, it was felt that this procedure represented the surgical method of choice for reversible collapse therapy in the treatment of pulmonary tuberculosis in children and adolescents with open cavities.

Hartenstein, Milwaukee.

Isoniazid Treatment of Tuberculosis in Children. Werner Schneidt, Monatsschr. Kinderh. **102**:385-387 (Aug.) 1954.

Oral isoniazid (Rimifon) in a dose of 10 mg/kg/day in three divided daily doses was given to 68 children with various forms of tuberculosis. Ages of patients ranged from 8 weeks to 15 years. Four patients died during treatment. Thirty-three children had primary tuberculosis (pulmonary), ten had serous tuberculous pleurisy, five had cavernous pulmonary tuberculosis, one had tuberculosis cutis papulonecrotica, and one had adhesive tuberculous peritonitis. Three patients had

miliary tuberculosis, two of whom were cured and in whom the development of tuberculous meningitis was prevented. Fifteen patients had tuberculous meningitis in combination with miliary tuberculosis, twelve of whom were cured. Of these 12 children 3 received oral isoniazid as the sole medication, while the others were also given intramuscular streptomycin. Intrathecal streptomycin was not used in any of the 68 patients.

The drug was tolerated well throughout this study, and the problem of drug resistance of the acid-fast organisms did not become acute in any of the patients treated.

The author believes that isoniazid should be used in the treatment of primary tuberculosis in children, especially to prevent miliary spread and with it meningitic involvement in young children. He furthermore feels that isoniazid represents an advancement in the successful treatment of other tuberculous lesions in children besides primary pulmonary tuberculosis.

HARTENSTEIN, Milwaukee.

Diseases of Blood, Heart and Blood Vessels, and Spleen

HETEROTOPIC ORIGIN OF BOTH CORONARY ARTERIES FROM PULMONARY ARTERY: REVIEW OF LITERATURE AND REPORT OF CASE NOT COMPLICATED BY ASSOCIATED DEFECTS. C. G. TEDESCHI and M. M. HELPERN, Pediatrics **14**:53 (July) 1954.

The case is presented of a 13-day-old white girl who at autopsy revealed heterotopic origin of both coronary arteries from the pulmonary artery. The anomaly was not complicated by associated defects. The literature on the subject, including four comparable cases, is reviewed.

FROM THE AUTHORS' SUMMARY.

CAUSATIVE FACTORS UNDERLYING CONGENITAL HEART MALFORMATIONS: I. PATENT DUCTUS ARTERIOSUS. RAY C. ANDERSON, Pediatrics **14**:143 (Aug.) 1954.

A study was made of 205 cases of patent ductus arteriosus in which the diagnosis had been confirmed at surgery. Detailed family information was obtained in 117 cases, of which 105 were "uncomplicated" cases, 4 had a history of maternal rubella, and 8 had an additional cardiac defect but a negative history for maternal rubella. In the "uncomplicated" group, there were 145 later-born siblings, 2 of whom had patent ductus arteriosus. No case of congenital heart defects were reported among the parents or the 25 children of patent ductus arteriosus patients.

No cases of cousin marriage were reported in the parents of the 111 cases for whom this information was available. Patent ductus arteriosus occurred in five sets of twins, all discordant with respect to the defect, and including two definitely uniovular pairs, two probably uniovular pairs, and one probably binovular pair. No evidence was found of a birth-order effect for patent ductus arteriosus cases, but a definite seasonal incidence was noted for cases associated with maternal rubella or having additional cardiac defects. The incidence of patent ductus arteriosus in the general population was estimated to lie between one in 2500 and one in 5000, with the true figure probably lying closer to the former.

It was concluded that there is a definite familial tendency to the occurrence of patent ductus arteriosus. The risk figure for the recurrence of congenital heart defects in later-born siblings is of the order of 1 in 50. It was suggested that patent ductus arteriosus is not an entity of single etiology but that it depends on various prenatal as well as possible natal factors.

FROM THE AUTHOR'S SUMMARY.

ON LYMPHOSARCOMA CELL LEUKEMIA. EUGENE STRANSKY and AMBROSIO REYES, Philippine J. Pediatrics **3**:30-34 (Jan.-March) 1954.

A case of lymphosarcoma-cell leukemia in a 13-year-old boy is discussed. The clinical and hematological symptoms of this rather rare but very instructive disease are described.

FROM THE AUTHORS' SUMMARY.

A SIX-YEAR SURVEY OF THE CASES SEEN AT A SCHOOL CARDIAC CLINIC. JOHN APLEY and C. BRUCE PERRY, Arch. Dis. Childhood **29**:317 (Aug.) 1954.

An analysis has been made of 1286 children referred to a cardiac clinic for school children from 1943 to 1948.

One hundred forty-eight were diagnosed as having past or present rheumatic heart disease. One hundred three were diagnosed as having congenital heart disease (ninety-five acyanotic). Three hundred three were diagnosed as having "functional" murmur.

KELLY, Milwaukee.

THE SYNDROME OF THE SUPERIOR VENA CAVA IN THE CHILD. G. DE MURALT and H. P. MENANO, Helvet paediat. acta **9**:109 (June) 1954.

The superior vena cava syndrome is an affection due to an obstruction in the superior vena cava causing a stasis of the blood back-flow to the heart. It is very rare in children. The authors review the four cases described in the literature and report a personal observation of a boy, aged 5 years, suffering from a nephrotic syndrome, in whom the vena cava syndrome was due to a superimposed thrombophlebitis. The physical signs (cyanosis of the face, a more pronounced edema of the face than of the body, marked dilatation of the abdomen and of the neck veins), the x-ray findings (thrombosis visible on the chest plate), and the electrocardiographic findings (signs of an acute cor pulmonale) made the clinical diagnosis possible. The diagnosis was confirmed by necropsy.

The frequency of thrombosis in children in general and its pathogenesis and treatment are discussed.

FROM THE AUTHORS' SUMMARY.

THE KLIPPEL-TRENAUNAY SYNDROME. M. MEIER, Schweiz. med. Wchnschr. **84**:736 (July 3) 1954.

This syndrome consists of plane angioma of the skin, varicose-like dilatation of the veins in a circumscript part of an extremity, and hypertrophy of soft tissues and skeleton of this region of the body. The history and present status of a 21-year-old man are given, with the changes of the left upper arm and shoulder. Angiomas were seen from earliest infancy, while vascular changes were not noted until examination for military service. A relationship is pointed out to the more frequently seen combination of plane angioma with accompanying hypertrophy of one part of the face involved. Usually the changes occur on the lower extremities and date back to earliest childhood. Neither pain nor functional disability occur. The abnormality falls readily within the presence of lesions designated by Tobler as "angio-osteo-hypertrophic syndrome.

AMBERG, Rochester, Minn.

THE PROBLEM OF VASCULAR THROMBOSIS OF HEMORRHAGES IN THE COURSE OF CORTICOADRENAL THERAPY. PAR Y. BOUNAMEAUX, H. VAN CAUWENBERGE, and J. ROSKAM, Schweiz. med. Wchnschr. **84**:789 (July 17) 1954.

In man and animal cortisone and corticotropin (ACTH) on prolonged administration first shorten then prolong the bleeding time, while sodium salicylate leads to immediate prolongation. The adhesiveness of the platelets in vitro is diminished more rapidly by corticotropin and salicylates than by cortisone. There is a tendency to a hypercoagulability on cortisone treatment, a tendency to hypocoagulability on sodium salicylate.

AMBERG, Rochester, Minn.

CHRONIC HYPOPLASTIC ANEMIA OF THE TYPE OF BLACKFAN-DIAMOND. C. MARINI and D. BORTESI, Clin. pediat. **36**:483 (July) 1954.

A 3½-year-old girl had been pale from birth, with red blood cell counts ranging between 1 and 2 million. The other bone marrow functions were normal. The anemia could not be explained on the basis of family history, diet, hemolysis, hemorrhages, leukemia, or infection. A diagnosis of chronic hypoplastic anemia as described by Blackfan and Diamond seemed justified. The giving of transfusions relieved the anemia for a while; it was found possible to prolong the interval between transfusions by giving injections of a posterior pituitary preparation (Postipofisi Richter).

HIGGINS, Boston.

GEOPHAGIA AND BANTI'S SYNDROME. A. MORINI and R. MENOZZI, Clin. pediat. **36**:537 (July) 1954.

Geophagia is much more frequent than is generally realized; it is a habit initiated at a time when there was an abnormal response of the sense of taste.

Fifteen cases of splenomegaly and anemia in geophagics are reported. Intestinal parasites, with possibly one exception, were not the cause of this Banti's syndrome. The incidence of Banti's syndrome in geophagics is too frequent to be an accidental finding.

HIGGINS, Boston.

ATYPICAL DUCTUS ARTERIOSUS DIAGNOSED BY CATHETERIZATION. ALBERTO VIGNAU and JORGE ZAPATA, Rev. chilena pediat. **25**:230 (Aug.) 1954.

A case of patent ductus arteriosus with atypical symptomatology is described. Catheterization of the ductus was an essential finding in establishing the diagnosis. The patient was operated on with success.

FROM THE AUTHORS' SUMMARY.

DIAGNOSIS OF ABNORMAL POSITION OF PULMONIC VEINS. P. JONXIS and F. BEEKHUIS, Maandschr. kindergeneesk. **22**:280 (Aug.) 1954.

It is possible to study the passage of intravenously injected methylene blue through the arterialized skin of the forehead with the aid of a reflection oxymeter, according to Brinkman. In healthy children the curve in which the stain passes through the skin is of a certain form. In the case of the left-to-right shunt the curve deviates from this normal form. In patients with a pulmonary vein discharging into the right auricle the stain injected into the right pulmonary artery will produce an abnormal curve; that injected into the left pulmonary, a normal one. The authors discuss two patients in whom this method of investigation was used.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat, and Ear

RECENT TRENDS IN THE MANAGEMENT OF ESOPHAGEAL STRICTURES. CLAUDE C. CODY III, Ann. Otol. Rhin. & Laryng. **63**:1120 (Dec.) 1954.

Cody advocates early esophagoscopy in patients who are suspected of having caustic esophageal burns. Esophagoscopy establishes whether the esophagus is involved or not and fixes the site of damage in those instances where burns have occurred. If evidence of esophageal burn is found, immediate daily dilatation with soft mercury-filled bougies is started. After approximately one month of dilatations have been carried out, a second esophagoscopy is done. Following this, periodic dilatations are performed at longer intervals.

The late burned cases with stricture can be classified as (*a*) short stricture, (*b*) long or multiple strictures, and (*c*) stricture responding poorly to prolonged dilatation. Cases with short esophageal stricture usually respond well to bouginage. Those with long or multiple strictures pose real problems. Gastrostomy is usually necessary so that retrograde dilatation can be carried out. For the cases in which the stricture responds poorly to prolonged dilatation, Cody frequently advises surgical resection ,although it is believed firmly that if there is any means of establishing and maintaining the continuity of the esophagus without surgery a great advantage has been realized over any surgical correction.

STEELE, Kansas City, Kan. [A. M. A. ARCH. OTOLARYNG.].

RETROPHARYNGEAL ABSCESS AS A COMPLICATION OF ACUTE MIDDLE EAR INFECTIONS. M. J. TAMARI and J. F. ORRICO, Eye, Ear, Nose & Throat Month. **33**:523 (Sept.) 1954.

Retropharyngeal abscess is reported as a postoperative complication in two infants with middle-ear and mastoid infections. The children were only 3 and 4 months old, respectively, at the onset of the infection, and the spread of the infection toward the pharynx in both cases was probably induced by progression of the inflammation along the bony and cartilagenous wall of the Eustachian tube. Both cases are reported in detail.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

THE "PEDIATRIC EAR" AND ANTIBIOTICS. ROBERT HENNER, Eye, Ear, Nose & Throat Month. **33**:530 (Sept.) 1954.

Sound otologic care seeks not only to heal a middle-ear infection and prevent intracranial complications but also to cause a return of normal hearing. All cases of acute otitis media should be treated with antibiotics.

Henner preferred the oral administration of penicillin because it may be administered over a long period of time, with relatively few side-reactions. This treatment must be continued over a prolonged period until the ear drum and the hearing are completely normal. The usual time for complete resolution is from 7 to 10 days but may extend to three or four weeks. Paracentesis is indicated if the ear drum remains thickened and swollen with bulging and if reduced hearing persists. The incidence of paracentesis should be less than 10%. In persistent cases, bacterial sensitivity tests are valuable. Mastoidectomy is indicated if symptoms indicate complications or if there is evidence of extension of the disease.

In cases of recurrent otitis media, the causative factors must be determined. The commonest cause is inadequate treatment of each acute attack. In cases such as this in which the x-ray examination does not reveal extensive destruction and in which no complications are present, the patient should be given intensive antibiotic therapy for three to four weeks. If recurrence develops again, complete mastoidectomy is indicated.

A search must be made for causative factors, such as enlarged adenoids, nasal allergy, or sinusitis. Recurrent acute disease may be simulated by attic lesions with cholesteatoma formation. The repeated acute exacerbations of chronic otitis media are surpressed with antibiotics, but the cholesteatoma continues to develop and may involve vital structures. Atticomastoidectomy is indicated in such cases to prevent loss of hearing and extension of the disease.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

TRACHEOTOMY: INDICATIONS AND COMMENTS. G. S. FITZ-HUGH and W. C. MORGAN JR., Eye, Ear, Nose & Throat Month. **33**:659 (Nov.) 1954.

The results of a study of 150 patients undergoing tracheotomy are presented with an analysis of the indication for which the procedures were performed. The following classification of the indications for tracheotomy is utilized: (1) fixed obstruction to upper airway (rapid obvious anoxia), (2) fluid obstruction to lower airway (slow obscure anoxia), and (3) prophylactic (to prevent 1 and/or 2).

The first group includes those patients with an obstruction at the laryngeal level of the air passage which could be bypassed by an opening in the trachea below the obstructive level, and represents the classical indication for tracheotomy.

In the second group the fluid mechanical obstruction may be caused by excessive accumulation of fluid material in the tracheobronchial tree from aspiration of oral fluids, hyperfunction of the secretory elements, or failure of the cough mechanism from various causes. In this group postural drainage, bronchoscopic and catheter aspirations, and aspiration by way of an endotracheal tube may give relief, but frequently tracheotomy becomes the procedure of choice. This fluid obstruction may occur in a variety of diseases and injuries, including trauma to the chest, neck, head, and spinal column, postoperative neurosurgical conditions, poliomyelitis, and tetanus.

With a better understanding of the clinical physiology of respiration and with greater experience in those diseases described in the second group, prophylactic tracheotomy is being performed more and more frequently. The establishment of a temporary airway by the insertion of an endotracheal tube or a bronchoscope transforms a disorderly, emergency type of tracheotomy into an orderly procedure. The vertical midline incision is used most often, but has little advantage over the horizontal incision, except in a true emergency. When the tracheal cartilage is incised, it is advisable to excise a small segment of the cartilage. Recently a plastic cannula has become available which is especially useful in those patients receiving x-ray irradiation therapy over the area of the tracheotomy. Fitz-Hugh and Morgan stress the fact that tracheotomy performed by skilled personnel is a surgical procedure involving little risk.

JENNES, Waterbury, Conn. [A. M. A. ARCH. OTOLARYNG.].

CONGENITAL DEAFNESS. A. A. J. VAN EGMOND, J. Laryng. & Otol. **68**:429 (July) 1954.

Congenital deafness is defined and classified and the distinction between acquired congenital deafness and inherited congenital deafness attempted. The influence of environmental, chemical, and physical factors must be known and borne in mind in addition to straight Mendelian concepts. Indeed, these environmental factors lend more promise from the standpoint of prevention (i. e., rubella deafness) than is offered in inherited congenital deafness where sterilization and social restrictions are the only weapons.

There are two types of congenital hereditary deafness, namely, dominant hereditary and recessive sporadic deafness. The former is rarely congenital, usually develops at middle age; it shows a strong tendency to progression for all pregnancies and according to its dominance will be present in every generation, with a chance of 50% of the offsprings.

Congenital sporadic recessive deafness may be combined with other disorders, such as disturbed vestibular function, retinitis pigmentosa, feeble-mindedness, and hereditary ataxia, and is commonly the product of consanguineous marriages (i. e., 7% of all deaf-mute children). Congenital hereditary deafness accounts for half to one-third of all the deaf, recessive deafness strongly predominating. In both types there is a lack of histopathological consistency of the structures involved. In general, in sporadic recessive deafness the cochlear bone is intact and there is a deficiency of the total acoustic nervous system. In dominant hereditary deafness the development of the cochlear bone is arrested with secondary defects of the nervous structures. In both, the organ of Corti is more or less damaged, and this explains the varying degrees of hearing loss encountered.

The deafness associated with congenital atresia of the external meatus, erythroblastosis fetalis, environmental factors (i. e., rubella), syphilis, and drugs such as quinine, the salicylates, and alcohol is discussed.

The prevention of congenital deafness is primarily a social, hygienic, and nutritional problem.

LeJeune and Normann, New Orleans [A. M. A. Arch. Otolaryng.].

The Pathology of Rubella Deafness. John Lindsay and R. Spencer Harrison, J. Laryng. & Otol. **68**:461 (July) 1954.

The production of fetal abnormalities depends more upon the timing and magnitude of the interference than the precise nature of the organism or agent. The same type of abnormality is producible by several methods—at least experimentally—provided they are applied at the same developmental stage, and it appears that for each part of the body there is a critical developmental period during which it would be selectively affected.

After the sixth week of pregnancy the vestibular system is spared. Between the 6th and the 12th week the cochlea appears to be more easily damaged; the organ of Corti is not completely developed until the end of the 5th month.

In Goodhill's series of 904 deaf children, rubella deafness was responsible for 20.5% as against 3% caused by erythroblastosis and 10% by meningitis.

Significant pathology in structures involved is infrequently demonstrable. The bony labyrinthine capsule is always normal, as are the utricle and semicircular canals. Reissner's membrane, the stria vascularis, saccule, and tectorial membrane all show marked, if variable changes. The cells of the spiral ganglion and Corti's organ are usually well preserved. The hair cells, however, are probably particularly affected by the lack of development in the apical regions, although this is difficult to demonstrate.

The changes in the cochlear duct appear to be secondary to the changes in the stria vascularis. This later structure may show considerable atrophy without any effect on hearing.

There is no evidence to indicate that hydrops ever occurs in these ears. It is difficult to explain the limitation of the changes to the cochlear duct and saccule.

LeJeune and Normann, New Orleans [A. M. A. Arch. Otolaryng.].

The Management of Epistaxis. William H. Evans, Laryngoscope **64**:911 (Nov.) 1954.

This is a broad review of the problem of epistaxis. It includes causes of the condition and the sites most encountered. Many substances used for the control of bleeding are mentioned. Management is discussed in detail, for both children and adults. The use of oxidized cellulose in large amounts is cautioned against. In one case a septal perforation resulted. In telangiectasis a rubber balloon is preferable to packing. X-ray treatment and electrocoagulation of the local area may be necessary.

Cortisone or corticotropin (ACTH) has been used successfully in purpura, chronic hypoplastic anemia, and pseudohemophilia.

Minor surgical procedures are sometimes resorted to. They include the elevation of the nasal mucosa and submucous resection. Occasionally one must ligate one or more of the major arteries. The techniques are described.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

AN EVALUATION OF CERTAIN THERAPEUTIC AGENTS AND PROCEDURES IN THE TREATMENT OF ACUTE DIFFUSE EXTERNAL OTITIS. B. H. SENTURIA, R. J. CROSS, J. E. LETT, and A. V. HARDY, Laryngoscope **64**:1001 (Dec.) 1954.

Three hundred eighty-six ears with acute diffuse external otitis were included in this study. Cultures and sensitivities were done on all. The agents tested were (1) oxytetracycline HCl, (2) polymyxin B sulfate, (3) 4-aminomethylbenzensulfonamide HCl, 5%, (4) nitrofurazone, (5) oxytetracycline HCl and polymyxin B sulfate, and (6) controls: (*a*) normal (0.85%) saline drops and (*b*) fatty acids in a wool fat vehicle.

The ear canal was cleaned and the agent applied either on a wick or by drops (less severe cases) every four hours. The agents were taken in order. If there was no improvement after several days, the agent was changed to that indicated by the sensitivity test. In general the results were discouraging. No particular agent stood out as particularly beneficial. Even cases treated with the controls sometimes responded as well. It was felt too that the importance of the in vitro sensitivity tests was questionable and should therefore only serve as a guide in treatment. Of note is that one of the authors (B. H. S.) feels that the Pseudomonas is not the primary offending organism but another, which lies deeply in the dermis. The treatment therefore might better be parenteral.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

BACTERIOLOGICAL STUDIES OF OTITIS EXTERNA—1951, 1952, AND 1953. ALBERT V. HARDY, MINNIE SCHREIBER, WARREN R. HOFFERT, ELIZABETH YAWN, ROLAND B. MITCHELL, and FLORENCE YOUNG, Laryngoscope **64**:1020 (Dec.) 1954.

The bacterial flora of the normal ear and the ear with external otitis was studied. The study was primarily a laboratory one. It was conducted during three summers (1951, 1952, and 1953) in Florida. Tables show the number and presence of each kind of bacteria in normal and infected ears for each year. Most outstanding was the predominance of the Pseudomonas group in the infected ears. It ran from 65%-88%. Next high was the coli-aerogenes group, then the Staphylococcus. Also prominent was the absence of mycological flora. Normal ears showed very little (1%-1.3%) Pseudomonas but a fair number of gamma-type streptococci and Staphylococcus albus.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

PRESCHOOL DETECTION OF DEAFNESS BY DOCTORS AND PARENTS: ITS IMPORTANCE IN PREVENTION, RESTORATION AND REHABILITATION. EDMUND PRINCE FOWLER SR., New York J. Med. **55**:797 (March 15) 1955.

This paper was one of a series of "lectures" on various subjects given by various authorities before the Annual Meeting of the New York State Medical Society during May, 1954. Fowler recalls the fact that deafness is reportable under the state laws, but that few seem to know or obey this law. The statute is "loosely drawn and has no teeth." Detection of early deafness is the responsibility of those nearest the child: mother, nurse, physician, and teacher. If a child playing on the floor takes no notice of the sound of fire engines, automobile horns, or noises in the home or shows no "startle reflex," he is suspect, and one must search for the lack of response. The baby should be tested surreptitiously or while out of sight of the noise source. While playing a game with the child, the mother may notice no or an inadequate response. The physician should have a history of affected siblings, or so-called "family deafness," having in mind a predisposition to heredity. Total deafness never recovers, and to look for a "miracle cure" is expensive, ridiculous, and nonproductive. One had better place the child in a part-time nursery school for the deaf, then graduate him to a resident school where lipreading and other methods are in use. The infectious diseases of childhood often leave a hearing loss, which should be determined by an otologist. It then becomes his duty to check such loss and to give treatments according to his judgment. There is "a large factor of chronicity" always present, and therefore early detection is paramount.

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura, and Mediastinum

INTERSTITIAL PLASMA CELL PNEUMONIA. S. D. STERNBERG and J. H. ROSENTHAL, J. Pediat. **46**:380-393 (April) 1955.

Interstitial plasma-cell pneumonia was first reported in the European literature in 1938. Since then there have been many reports of this disease from Germany, Switzerland, the Scandinavian countries, and recently the first American report, from Milwaukee. It mostly affects premature and dystrophic mature infants under the age of 6 months.

The disease gets its name from findings at autopsy: Small interstitial pulmonary infiltration by mononuclear cells that look like plasma cells. There are no inclusion bodies.

The onset of the disease is insidious, with lassitude, vomiting, and difficult feeding. The infant may be afebrile. There is increased respiratory distress, often without reason from the stethoscope. There may be a leucocytosis with normal differential.

X-ray is typical—even in cases that have few clinical signs—with confluent, hazy, milk-like opacity, spreading from the hilum to the periphery of the lungs. Fibrotic residual streaking may persist for four to five months after clinical recovery.

The authors report four cases; all recovered. The cause is not known. Treatment is supportive.

MACDONALD, Pittsburgh.

THE ROENTGEN DIAGNOSIS OF NONOPAQUE FOREIGN BODIES IN THE BRONCHI. FREDERICK ELIAS, New York J. Med. **55**:1461 (May 15) 1955.

Elias states that fully 50% of all foreign bodies aspirated are nonopaque and occur chiefly in children under 3 years. Two cases are cited to uphold this thesis. History is of first importance, but may not be elicited. There are coughing and difficult breathing following sudden onset. Wheezing is common. There may a "symptomless interval" (Jackson and Jackson). Physical examination tells little, but there is a limitation of lung expansion on the affected side, with an associated emphysema or atelectasis. Obstructive emphysema in a young child points to foreign-body suspect. Confusion with bronchopneumonia, unresolved pneumonia, tuberculosis, lung abscess, bronchiectasis, and laryngotracheobronchitis is not unlikely. Early x-ray diagnosis is paramount in order that removal of the foreign body be prompt before pathological changes take place in the lower airways. Vegetable matter (peanuts) produces severe symptoms, which often are completely masked. Jackson has called frequent attention to peanut brittle when inhaled by small children as a concomitant cause. The important item is to hold under foreign-body suspicion all small children with symptoms and signs of lower respiratory obstruction.

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

GENERALIZED CYTOMEGALY AND LOCALIZED "PNEUMOCYSTIC" FORMATION IN A CASE OF INTERSTITIAL, PLASMACELLULAR PNEUMONIA IN EARLY INFANCY. K. WEISSE, Ztschr. Kinderh. **76**:27, 1955.

The author describes a case of generalized cytomegaly with acidophilic inclusion bodies in brain and lungs and "pneumocystic" formations (Carinii). The etiology is believed to be a virus producing interstitial pneumonia and meningoencephalitic changes. GLASER, Baltimore.

Nervous Diseases

SOME OBSERVATIONS ON BRAIN ABSCESS. E. A. STUART, F. H. O'BRIEN, and W. J. MCNALLY, A. M. A. Arch. Otolaryng. **61**:212 (Feb.) 1955.

The authors report their findings in a study of 125 patients having a pyogenic abscess of the brain, verified by operation or autopsy. They noted that otitis media with mastoiditis was the most frequent single cause of intracranial abscess. Brain abscess developed in 0.5% of the acute middle ear infections and in 3% of the cases of chronic otitis media. In general, the abscess was located in the part of the brain which was contiguous with the site of primary infection, most usually the temporal lobe on the affected side. Contralateral single or multiple abscesses in the parietal or temporal lobe were encountered occasionally. Chronic otitis media was the most frequent cause of cerebellar abscess, and was usually ipsilateral. In contrast to chronic middle ear infections, acute infections of the paranasal sinuses were the second commonest cause of

intracranial abscess. The frontal lobes were affected most frequently secondary to frontal sinusitis. Of the 125 cases, there were 18 of intracranial abscess which was disseminated from a remote site. The lung was the commonest source of dissemination to the cerebrum, usually in the temporal, parietal, or occipital lobe, but not to the cerebellum. There were also 22 cases in which the source was undetermined but which may have been due to infected teeth or pneumonia. In other instances there were signs of cerebral involvement, consisting of seizures, hemiparesis, aphasia, and indications of meningeal irritation but in which no abscess was encountered. The authors suggest that these symptoms may have been due to cerebral venous thrombosis or thrombophlebitis. With the advances of antibacterial therapy, some infections are arrested in the vascular stages which otherwise may have progressed to form brain abscess.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

SPINAL CORD TUMOR IN A NEWBORN. DWIGHT PARKINSON, HARRY MEDOVY, and J. R. MITCHELL, J. Neurosurg. **11**:629, 1954.

The authors report a case of a spinal cord tumor in a newborn infant which was detected at birth when neurological examination revealed a sensory level at T 11. Surgery was performed after myelography revealed a complete block at T 8, and a malignant glioma, possibly a neuroepithelioma, was completely removed. The child has shown improvement postoperatively.

Spinal cord tumors are rare in childhood, particularly in infancy. The authors have been unable to find any recorded case of a spinal cord tumor, other than teratoma and dermoid, which was evident at birth.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

DECEREBRATE STATE IN CHILDREN AND ADOLESCENTS. ROBERT C. L. ROBERTSON and CLAUDE POLLARD JR., J. Neurosurg. **12**:13, 1955.

The clinical signs of decerebrate rigidity are seen frequently in humans as a result of traumatic or vascular lesions. The characteristic neurologic signs of profound unconsciousness, pinpoint pupils, extensor rigidity in the arms and legs, and bilateral Babinski sign are indicative of a severe lesion at midbrain level, which is associated with a more or less hopeless prognosis.

The authors reported 13 unselected cases of decerebrate rigidity from varying causes with ages ranging from 2 to 57 years and found that the children in this group who were able to survive the immediate decerebrate state had a much better prognosis than the adults. Six of the 13 children and adolescents are relatively normal neurologically, as compared with none of the 13 adults who showed similar decerebrate states. However, the initial mortality of the decerebrate state in children is probably higher than in adults. Tracheotomy is advocated as an early measure to control respiratory obstruction secondary to secretions, which may lead to hypoxia and increase the neurologic deficit.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE ROENTGENOGRAPHIC DIAGNOSIS OF THE ARNOLD-CHIARI MALFORMATION. R. SHAPIRO and F. ROBINSON, Radiology **73**:390 (March) 1955.

The Arnold-Chiari malformation is a downward transposition of the cerebellum and medulla to the cervical portion of the spinal canal. Shapiro and Robinson report the myelographic findings in a case of the malformation which they have seen and compared them with myelographic findings in two cases of cervical meningioma. All three cases presented a somewhat similar clinical picture, consisting of the symptoms and signs of cord compression high in the cervical region. Shapiro and Robinson believed that in the pure, uncomplicated Arnold type of malformation cervical myelograms should demonstrate an obstructive cervical lesion with an inferior bilobulated border, which is caused by the inferior margin of the herniated cerebellar hemispheres. However, since dense adhesions are frequently present over the cord in association with the Arnold-Chiari malformation, one cannot depend on demonstrating the typical picture. The combined Arnold-Chiari deformity results in buckling and downward displacement of the medulla against the cervical cord. The pressure of the medulla may cause a complete block of the opaque myelographic medium, and the typical bilobulate pattern produced by the herniated cerebellar hemispheres may not be seen. The differential roentgen diagnosis of these defects in the myelograms of children and adolescents is not difficult, because high spinal cord tumors

in this age group are uncommon. The coexistence of such a myelographic finding with hydrocephalus favors the diagnosis of the Arnold-Chiari malformation. In adults the problem is much more difficult, since many other diseases must be considered in the differential diagnosis.

WEILAND, Grove City, Pa. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

MORPHOLOGICAL NERVOUS CHANGES IN SURVIVORS OF SEVERE JAUNDICE OF THE NEWBORN. L. CROME, J. Neurol., Neurosurg. & Psychiat. **18**:17, 1955.

Crome reports the central nervous system changes in two infants who had severe jaundice at birth secondary to Rh sensitization and who died at the ages of 19 and 20 months, after they had survived the initial period of jaundice. Both patients had serological Rh-factor incompatibility, neonatal jaundice, and erythroblastosis clinically. After recovery they developed neurological manifestations (intermittent rigidity and tremor of the hands; inability to speak, walk, or talk, and epilepsy, in the second case only). Death was due to status epilepticus in the second case.

Neuropathologic study revealed widespread loss of nerve cells throughout the cortex, involving particularly Layers II and III. The nerve cells stained unevenly, being either hypo- or hyperchromatic. Nissl substance was lost in many cells, and "ghost cells" were evident throughout. The other morphological feature of importance was the lack of myelination in the putamen and radial bundles of the globus pallidus. The corpus Luysii was involved in one of the cases. Fibrous gliosis was noted in the globus pallidus as well.

MANDEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Psychology and Psychiatry

PARENT-CHILD RELATIONSHIPS. CHARLES H. CUTLER, California Med. **83**:17 (July) 1955.

Parents and doctors have an obligation to supply children with an emotional diet leading to their eventual maturity. This is as important to the child as is his physical guidance. The proteins, carbohydrates, fats, minerals, and vitamins of a child's emotional diet are (1) the need for security; (2) the need to achieve social adaptability; (3) the need for success, and (4) the need for independence. In helping parents provide their children with these major guideposts along the road of character development toward maturity, physicians have a challenge and opportunity for real service to the humanities—a field of endeavor far behind science in human progress.

PRYOR, Redwood City, Calif.

THE CLASSROOM TEACHER'S ACTIVITIES AND ATTITUDES RELATING TO SPEECH CORRECTION. GRETCHEN WRIGHT LLOYD and STANLEY AINSWORTH, J. Speech & Hearing Disorders **19**:244-249 (June) 1954.

Fifty-five regular teachers in two countries were interviewed concerning their knowledge of and activities in speech correction. Teachers know very little about such activities even so far as failure to refer known cases. Most of the difficulty lies apparently in inadequate training rather than in fundamental attitudes of the teacher.

PALMER, Wichita, Kan.

THE SOCIAL POSITION OF THE SPEECH DEFECTIVE CHILD. ELINOR HORWITZ PERRIN, J. Speech & Hearing Disorders **19**:250-252 (June) 1954.

The author states that many speech-defective children are not readily accepted members of their classroom group and form actual isolates in the social population.

PALMER, Wichita, Kan.

PHYSIOLOGICAL DAMAGE UNDER EMOTIONAL STRESS AS A FUNCTION OF EARLY EXPERIENCE. OTTO WEININGER, Science **119**:285 (Feb. 26) 1954.

Studies by the author have indicated that the more albino rats are handled and petted the better they seem to thrive in a laboratory situation. He also presents data to show that such rats grew better and exhibited less evidence of cardiovascular and gastrointestinal damage in

response to a standardized stress situation consisting of immobilization and starvation for 48 hours. Responses indicating fearful behavior to an open-field situation revealed a much less clear-cut difference between the gentled and nongentled animals.

FORBES, Rochester, N. Y.

A STUDY OF THE PSYCHOLOGICAL ASPECTS OF A CASE OF ULCERATIVE COLITIS. ROBIN HIGGINS, Great Ormond St. J. (No. 8) pp. 99-104, 1954-1955.

The manner in which a psychosomatic disorder may develop in a child and the influence that the family history may exert on the development are discussed, along with points to be considered in the treatment of a case of ulcerative colitis in a 9½-year-old girl.

MCGUIGAN, Evanston, Ill.

SOCIAL REASONS FOR PLAY IN INFANCY. CARMEN ISERN GALCERAN, Arch. pediat., Barcelona **5**:243-256 (Nov.-Dec.) 1954.

The author outlines the physical and psychosexual development in children, giving due credit to Gesell and Freud as well as others in this field. She is especially interested in the use of play to develop senses to their fullest in order that they may understand and use their environment as a normal way of release and satisfaction. The development from a helpless infant dependent wholly on the mother to a socially acceptable individual is outlined. It is important that no stage of development be skipped. She also urges parents to enjoy and participate with their children; and comments that no one who doesn't love children will have much success in assisting in their growth and development.

ALLEN, Santa Fe, N. Mex.

THE ORIGIN OF BEHAVIOR DISORDERS IN CHILDREN. C. BENNHOLDT-THOMSEN, Deutsche med. Wchnschr. **79**:1326 (Sept. 3) 1954.

A few interesting cases are reported illustrating psychosomatic and somatopsychic sources of various symptoms with attention to polyetiologic features.

AMBERG, Rochester, Minn.

Diseases of Genitourinary Tract

VULVAR FUSION IN INFANCY AND CHILDHOOD. NOAH BARYSH, New England J. Med. **250**:637 (April 15) 1954.

Fusion of the labia minora by virtue of their close approximation and high intrinsic cellularity is common in infancy and childhood, although it is mentioned only briefly in the general pediatric literature. Failure to examine the vulva of the immature girl and to correct the abnormality may lead to erroneous diagnoses in adolescence. The psychologic implications are obvious.

The abnormality is ordinarily without subjective symptoms, although an occasional older child may have secondary urinary complication. The thin membrane may be gently separated in young girl babies without anesthesia. Older children may require analgesia, and the parents should be carefully informed that the patient's hymen is not being ruptured. Mild lubricants will prevent a recurrence.

Four cases are presented, illustrating the psychologic and anatomic features.

WHEELOCK, Denver.

STUDY OF THE BLOOD SERUM OF CHILDREN WITH LIPOID NEPHROSIS DURING THE PERIOD OF EVOLUTION TOWARDS RECOVERY. C. HOOFT and R. CLARA, Ann. paediat. **182**:334 (May) 1954.

The serums of six children with lipoid nephrosis have been studied during the period of recovery. In three cases the recovery occurred in a very short lapse of time. The period of evolution to recovery was characterized by a quick normalization of all the protein fractions. Three other children with a lipoid nephrosis of the chronic type have been studied during the same period; in one case the percentage distribution and the absolute values of the different fractions normalized only gradually; in a scecond case the recovery has been obtained a few weeks after an infection with measles; in a third case the period of recovery lasted a long time and was introduced by a serum hepatitis.

In the last two cases an increase of the γ-globulin level preceded the normalization of the other protein fractions.

FROM THE AUTHORS' SUMMARY.

OVARIAN TUMORS IN CHILDREN. ANNE-MARIE STECK, Helvetica paediat. acta **9**:69 (April) 1954.

Tumors of the ovaries are not extremely rare in childhood and are often not diagnosed as such. In the last 20 years, 19 cases of tumor of the ovaries have been observed in the surgical department of the Kinderspital in Zurich, only one of which was received at the hospital with the correct diagnosis. The 19 cases showed the following distribution of tumor types: 6 cases of single or multiple cyst, 2 parovarian cysts, 6 dermoid cysts, 1 teratoma, 1 dysgerminoma, and 1 metastatic tumor. The dermoid cysts and the single cyst are the commonest ovarian tumors in childhood. According to the literature the polycystic ovaries appear to be very common and generally without pathological consequence. Our cases show two types of clinical picture. In four cases an abdominal tumor is the main feature. Its relation with the adnexae, its mobility which may be considerable, and the characteristic finding at x-ray of teeth and other calcifications lead one to suspect an ovarian origin. In the 15 other cases a symptomatology of acute abdomen arising usually from pedicle torsion was the reason for admission with the diagnosis of acute appendicitis. The very sudden and intense nature of the pain, often accompanied by vomiting and a state of shock, and the discovery of an adnexial tumor after careful palpation make it possible in most cases to clarify the diagnosis before operation. As a last resort the finding at operation of an hemorrhagic exudate makes it necessary to examine the adnexae. The differential diagnosis, including the nontumoral ailments of the adnexae in children, such as torsion of healthy ovary, follicular rupture, and inflammation of the adnexae, is discussed in detail.

FROM THE AUTHOR'S SUMMARY.

CREATININE TOLERANCE TEST AS A RENAL FUNCTION TEST. ELI NORBYE, Acta pædiat. **43**:113 (March) 1954.

A renal function test with creatinine tolerance determination has been employed in accordance with a method described by Sundal. The method seems to be a simple and reliable method, easily managed, and shows good correspondence with other renal function tests.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL VALVULAR FORMATION OF THE POSTERIOR URETHRA. K. H. TORP, Acta pædiat. **43**:192 (March) 1954.

Four fatal cases of congenital valvular formation of the posterior urethra in boys are reported, two of which presented greatly dilated urinary tract at birth and simultaneously cryptorchism.

FROM THE AUTHOR'S SUMMARY.

Diseases of Ductless Glands; Endocrinology

STUDIES OF ACTH UPON PERFUSED BOVINE ADRENALS: DURATION OF ACTH ACTION. I. A. MACCHI and O. HECHTER, Endocrinology **55**:434-438 (Oct.) 1954.

The necessity for a constant supply of circulating corticotropin (ACTH) for maximal adrenal stimulation in the human is in basic agreement with the similar findings in this in vitro study.

JACOBSEN, Buffalo.

PLASMA 17-KETOSTEROIDS OF THE HUMAN FETUS: DEMONSTRATION OF CONCENTRATION GRADIENT BETWEEN CORD AND MATERNAL CIRCULATIONS. L. I. GARDNER and R. I. WALTON, Helvet. paediat. act. **9**:311 (Oct.) 1954.

Neutral 17-ketosteroids have been measured in the plasma of pregnant women at the time of delivery and in cord plasma obtained immediately thereafter. The data show an increased concentration of neutral 17-ketosteroids in the fetal circulation when compared with the maternal.

The data are interpreted to indicate that the elevated plasma 17-ketosteroids of the newborn infant are derived from some tissue in the fetal circulation rather than from the mother. The most likely sources are considered to be the inner cortex of the fetal adrenal and/or the placenta.

Evidence is presented which supports the concept that the inner cortex of the fetal adrenal is maintained by the fetal hypophysis. It is hypothesized that placental estrogen causes discharge of luteinizing hormone (LH) from the fetal hypophysis, the estrogen having its effect mediated through the neurohypophysis. The LH in turn maintains the internal cortex of the fetal adrenal.

FROM THE AUTHORS' SUMMARY.

CLINICAL, ANATOMICAL AND RADIOLOGICAL OBSERVATIONS AS TO THE IMPORTANCE OF THE THYMUS IN INFANT PATHOLOGY. C. TORRICELLI and G. BIZZI, Lattante **25**:224 (April) 1954.

X-ray examinations of 100 normal healthy infants revealed a visible thymic shadow in 65 cases; but in only 7 of these were the shadows very large. There was a visible thymic shadow in only 22 of 50 immature infants; the conclusion seems justified that the incidence of an enlarged thymic shadow is much less in the immature child.

Of 112 radiograms showing enlarged thymus glands, in only 32 cases did the patient have clinical symptoms.

When an enlargement of the thymus gland was found at autopsy, there was also hyperplasia of the spleen and lymph nodes and hypoplasia of the adrenal glands. In only five of nine cases where the infant died suddenly, was the thymus gland enlarged, and in only two of these could no other pathological cause for the death be established.

HIGGINS, Boston.

SEVENTY-THREE CASES OF THYMIC HYPERPLASIA. P. MENGHI and P. BRUSA, Minerva pediat. **6**:84 (Feb. 15) 1954.

Seventy-three children with thymic hyperplasia have been observed in the pediatric clinic in Milan during the past six years. Fifty-eight of the children were under 6 months of age and only five over 1 year old. Twenty-eight children had cyanosis, twenty-three dyspnea, eleven convulsions, six troublesome coughing, six vomiting, and eight pallor or apnea. Twenty children were free of symptoms; it hardly seemed necessary to treat the symptom-free cases.

HIGGINS, Boston.

THE IMPORTANCE OF DETERMINING THE URINARY 17-KETOSTEROIDS IN VARIOUS MORBID CONDITIONS OF CHILDREN. S. SCARABICCHI, Minerva pediat. **6**:95 (Feb. 15) 1954.

The 24-hour excretion of 17-ketosteroids was determined in the urine of 110 children with various disorders of growth, glandular dyscrasias, or renal, blood, or muscle disease. The determinations are shown to be of definite diagnostic value in recognizing disease of the pituitary gland, the gonads, or the adrenal glands.

HIGGINS, Boston.

CHORIONIC GONADOTROPIN WHICH PROVIDES A NEW MEANS OF TREATMENT IN CASES OF EXCESSIVE FAT IN HUMAN MILK. MICHELLE PARADISO and CARMELO LA CAUZA, Riv. clin. pediat. **54**:122 (Aug.) 1954.

The authors treated 20 wet-nurses with very fat milk with 500 units chorionic gonadotropin doses, administered intramuscularly every second day, reaching a total dose of 2000 units (four injections).

After such treatment the milk fat content lowered, in every case, to normal values or scarcely higher than the average, while the level of other components, lactose and proteins, did not reveal marked changes. In 10 nurses the fat content remained normal until two months after the beginning of the treatment.

In the remaining 10 cases the fat content showed a more or less strong tendency to rise again, turning toward the starting values.

An additional treatment with chorionic gonadotropin allowed the fat content to remain lowered in almost every case within the normal values or at least well tolerated by the infant.

It was possible to observe strictly such findings until one month after the end of the additional therapy cycles only.

FROM THE AUTHORS' SUMMARY.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

THE ROENTGEN FEATURES OF MUSCULAR DYSTROPHY. ALEXANDER LEWITAN and LOUIS NATHANSON, Am. J. Roentgenol. **73**:226 (Feb.) 1955.

The authors present a summary of 35 cases seen over a period of 15 years. This is a disease of unknown origin infecting myoneural junction and resulting in progressive wasting of musculature. Pseudohypertrophy of affected musculature is sometimes noted. The disease usually starts in childhood, occasionally starting during adolescence or puberty. It is primarily an affection of muscle, and changes within the muscle proper are the main radiographic features. These changes represent abundant replacement of muscle tissue by fat, which is seen radiographically as translucent shadows within muscle fascia. Degeneration of muscle tissue with replacement of fat occurs in other diseases, such as in polio, however, there are certain distinguishing features, as follows:

1. Muscle volume in muscular dystrophy is either maintained as the disease progresses and is replaced by fat, or the muscle volume is increased in the pseudohypertrophic form, whereas in the wasting diseases muscle volume is reduced.

2. Involvement of the osseous system. Concentric atrophy, seen only when the disease begins prior to epiphyseal closing, consists of reduction in width of the medulary canals of long bones. It can occur, however, in any disease permanently affecting any part of the afferent or efferent nervous supply in children at an early age. Epiphyseal development of bone is responsible for longitudinal growth, but growth in width depends on stimulus and activity of healthy muscle, which is absent in this disease.

3. Secondary affection of joints with development of contractures due to the assumption of fixed positions for long periods of time and associated fibrosis in muscle resulting in shortening of tendons occurs.

4. The involvement of the spine, because of the weakness of the trunk musculature, is commonly seen with resultont scoliosis.

5. Other organs involved are:

(*a*) The heart has fat deposition with replacement by fibrous and scar tissue as can be seen post mortem.

(*b*) Muscular changes occur in the G. I. tract, but are not diagnosed by x-ray.

(*c*) The diaphragms which show limited excursion of the leaves are noted late in the disease, and associated with this basilar atelectasis and pneumonitis are not uncommon.

ALTMAN, Miami, Fla.

FRACTURES OF THE UPPER EXTREMITY IN CHILDREN. JOHN C. IVINS, Minnesota Med. **38**:296 (May) 1955.

Good fracture treatment in children produces better results than with comparable fractures in the adult. The heavy periosteum that surrounds the bone in children aids in the closed reduction. The potential of rapid growth in the young bone aids in producing a good result even after a mediocre reduction. The author makes a plea for conservatism in treating fractures in children.

STOESSER, Minneapolis.

EVALUATION OF SKELETAL AGE METHOD OF ESTIMATING CHILDREN'S DEVELOPMENT: II. VARIABLE ERRORS IN THE ASSESSMENT OF ROENTGENOGRAMS. DONALD MAINLAND, Pediatrics **13**:165 (Feb.) 1954.

An observer's variable error in skeletal age assessment of hand roentgenograms (i. e., the irregular variation between independent readings of the same film) was studied on 1124 readings of 326 films from 233 children aged 16 months to 17 years. Of the roentgenograms, 79 were full-sized reproductions in Macy's "Nutrition and Chemical Growth in Childhood," the remainder were actual films of children in Halifax, Canada (healthy orphanage residents and children examined in a nutrition survey).

There was no significant difference in variable error associated with the atlas (Todd, Greulich-Pyle), age of child, sex, differences between skeletal and chronological age, differences between children, or differences between roentgenograms of the same child, except for a tendency

in the Macy series for the poorest reproductions to have a larger variable error than the best reproductions. In most readings, the individual indicators were assessed separately and the results averaged, but a quicker method (over-all appraisal) did not produce a significantly different variable error. The quick method may be useful in large surveys, although it appears too coarse for the study of individual children.

The observer's variable error was expressed by standard deviations of approximately three months (Macy series—both atlases; Nutrition Series—Greulich-Pyle atlas) and four months (Orphanage Series—both atlases). With a standard deviation of three months, an assessor must affix an error of ±8.3 months to his estimate of a child's progress in skeletal age, in order to obtain limits with 95% probability. If his standard deviation is four months he must allow ±11.1 months. For evaluation of the assessment method, many observers' estimates of variable error are needed, and an appeal for data is issued.

After more than 1200 headings had been made, the observer's practice lapsed for about a year. Reassessment of a random sample of roentgenograms then showed, besides variable error, a mean systematic difference of approximately three months from the previous readings of the same films with the same atlas. To avoid this risk, any two films that are to be assessed for skeletal progress should be read within a few weeks of each other, and special precautions are therefore necessary to secure independence of the two readings.

FROM THE AUTHOR'S SUMMARY.

A FATAL CASE OF HEREDITARY EPIDERMOLYSIS BULLOSA. E. LUCINI, Lattante **26**:39 (Jan.) 1955.

An illegitimate baby girl showed bullous skin lesions from the age of one day. The lesions would heal without scarring, but other lesions were continuously replacing them. The infant gained slowly in weight for about one month; then the lesions began to be infected; antibiotic therapy was soon not efficacious. The child had fever and loss of weight and became dystrophic. She died at the age of 72 days. Wassermann tests on both the mother and the child were negative. The child had a dysproteinemia, characterized by low albuminemia, a low albumin: globulin ratio, and a marked increase in the alpha but not in the beta and gamma globulins. Colored pictures of the child and sections of the skin are presented. Although the case seemed to fall into the category of the hereditary cases of epidermolysis bullosa, the family history in this case, although meager, is negative. This is the 1st case of this condition reported from Italy and the 40th case listed in the world literature.

HIGGINS, Boston.

FRAGILITAS OSSEA CONGENITA. ANTONIO RICHINI and MARCELLO GIUSTI, Riv. clin. pediat. **54**:313 (Nov.) 1954.

Etiologic and pathogenetic theories, pathologic anatomy, clinical picture, and actual acquisition of congenital osteogenesis imperfecta have been investigated.

Five cases examined by the authors are reported; a detailed anatomic and histologic study on endocrine glands, liver, kidney, and bones of one of these cases is described.

On the basis of their histological findings the authors think that the osteogenesis imperfecta is likely to have a corticosuprarenal origin, owing to the action of some hormones, of the cortisone type, inhibiting the growth of a normal fundamental substance.

Moreover, on the basis of their clinical experience, the authors suggest that Vroloch and Lobstein diseases ought not to be distinguished from one another and be regarded as distinct manifestations of the same disease, and therefore they consider it a congenital bone fragility either precocious or late according to the time of occurrence.

The authors describe the treatment of two cases, suffering at birth from congenital bone fragility and still living, whose bones and general health conditions are satisfactory.

FROM THE AUTHORS' SUMMARY.

A CASE OF CONGENITAL DERMAL SINUS. F. ALTOGANO, Acta pediát. españ. **12**:467-477 (May) 1954.

The author reviews the literature on dermal sinuses and remarks that they are almost always associated with an occult spina bifida. Frequently these things are overlooked and trouble develops. Early extirpation is far better than simply waiting for an infection.

The case presented is a 2-year-old boy brought in with acute meningitis. He had a dermal sinus complicated by cystic type of spina bifida occulta.

Diagnostic procedures are described, with x-rays taken, methods of treatment, and comments on the complications, such as meningitis and subdural and subarachnoid abscesses, which may develop if surgical intervention is not done.

ALLEN, Santa Fe, N. Mex.

PSEUDOARTHROSIS APLASTICA OF THE ELBOW: OSTEOLYSIS WITH NEUROFIBROMATOSIS. P. PINLACHS and P. CALLAFELL, Rev. españ. pediat. **10**:1-14 (Jan.-Feb.) 1954.

The authors present the case of a fracture in the radius and ulna with failure to heal. The study is accompanied by x-rays of all the long bones. The abnormalities noted were the pseudoarthrosis aplastica of the elbow with osteolytic process between the joint and the site of fracture.

Other signs of neurofibromatosis were noted, such as cutaneous lesions with pigmentation.

The authors state that in deformities resulting from fractures and in poorly healed fractures neurofibromatosis should be considered.

ALLEN, Santa Fe, N. Mex.

TREATMENT OF WARTS ON THE FOOT WITH LIQUID NITROGEN. P. ZIERZ, Med. Klin. **50**:710 (April) 1955.

Warts on the foot are frequently seen in children and adolescents. They are rarely combined with warts elsewhere. The foot warts are very painful on walking. Various forms of treatment are discussed. Liquid nitrogen has been displaced by carbon dioxide now, but at present liquid nitrogen is readily obtainable and offers definite advantages. The technique of application by a cotton carrier is described as well as the handling of the liquid nitrogen. Altogether 62 patients were treated with one to three applications, all successfully. In the age group of 4-14 years were 34 patients, none requiring more than two applications.

AMBERG, Rochester, Minn.

Teeth and Dentistry

DENTAL CARIES IN THE ALBINO RAT ON FLUORIDATED AND DISTILLED WATER. WINFREY WYNN and JOHN HALDI, J. Nutrition **55**:235 (Feb. 10) 1955.

Winfrey Wynn and John Haldi from their experiment concluded that drinking water containing 0.7 to 1 ppm of fluoride had no protective influence on experimental dental caries in albino rats fed a cariogenic diet.

FREDEEN, Kansas City, Mo.

UTILIZABILITY OF FLUORINE FOR STORAGE IN THE RAT WHEN ADMINISTERED IN MILK. JOSEPH C. MUHLER and DONOVAN A. WEDDLE, J. Nutrition **55**:347 (Feb. 10) 1955.

Joseph C. Muhler and Donovan A. Weddle in their data provided evidence that fluorine in concentrations suitable for routine human consumption cannot be placed in milk and still retain a satisfactory degree of metabolic availability.

FREDEEN, Kansas City, Mo.

FLUORIDATION. F. B. EXNER, Northwest Med. **54**:721 (July) 1955.

This is a very interesting and thought-provoking article presenting "the other side" of the fluoridation controversy. The author is a most sincere, conscientious, and honest roentgenologist, a respected member of the medical profession who does not believe in fluoridation of the public water supply.

This article should be read by everyone interested in the problem of fluoridation.

DOCTER, Seattle.

Miscellaneous

THE EFFECT OF ANALGESICS AND ANESTHETICS ON FETAL MORTALITY. PAUL W. SEARLES, Illinois M. J. **105**:243-245 (May) 1954.

In this article the plea is made for the use of nonasphyxiating mixtures of anesthetics with special care to administer adequate concentration of oxygen as far as both the mother and the infant are concerned in labor. If saddle-block or caudal anesthesia is used, maternal blood pressure must be checked and maintained at all times to avoid fetal anoxia.

The fundamental pathological lesion of asphyxia neonatorum clinically is complete atelectasis. The absence of negative intrapleural pressure in the infant who had never breathed is the reason why ordinary methods of artificial respiration are of no value in asphyxia of the newborn. Stimulant drugs have no place in the treatment asphyxia of the newborn. An intrathecal catheter or a bronchoscope should be passed and gentle suction carried out. Following suction an intermittent, low positive pressure should be applied until respirations of the infant have been established, after which continuous inhalation of oxygen can be administered until resuscitation is complete.

BARBOUR, Peoria, Ill.

FACTORS IN INFANT CARE. HEYWORTH N. SANFORD, Illinois M. J. **105**:246-248 (May) 1954.

In this treatise Sanford discusses the causes of infant mortality as they were enumerated in a study by Bundesen, Potter, and co-workers about a year ago.

Of the total deaths, 35% occurred in the first day of life, 33.7% occurred during the remainder of the first month of life, and 30.5% during the last 11 months of the first year.

The causes of death were as follows: (1) The greatest cause of infant mortality is abnormal pulmonary ventilation. Abnormal pulmonary ventilation is usually seen in two conditions, atelectasis and pulmonary hyaline membrane. The treatment of the atelectasis depends upon whether it is confined to one or two lobes because of an obstructed bronchus, or whether it is scattered throughout the lung. For hyaline membranes a detergent added to oxygen in a humid atmosphere is indicated. Another problem is the child born by Caesarean section. He never breathes as well as a normal baby. These babies tend to have an excessive amount of fluids, with edema of the brain and edema in different parts of the body. (2) Among birth accidents the second cause of infant mortality, cerebral hemorrhage, is very difficult to diagnose. (3) Malformation. There are three types of malformation common in the newborn—the nervous system, the cardiac system, and the gastrointestinal system. These three abnormal conditions will cover 85% of the mortality found in the newborn period. (4) Infection is the cause of 6.1% of infant mortality. (5) Blood disturbances cause only 2% or 3% of the mortality in the newborn.

BARBOUR, Peoria, Ill.

TWO SIMPLE OFFICE TECHNIQUES IN PEDIATRIC PRACTICE. F. MICHAEL SMITH and SARAH MARK BRAUD, J. Louisiana M. Soc. **106**:212-214 (June) 1954.

Smith and Braud review a simple office procedure for dealing with immobilization of clavicular fractures in infants and a simple technique for treatment of granuloma of the umbilicus. For the first a diaper method for posterior figure-of-eight immobilization is described, and for the second a cotton ligature method is explained.

MCGUIGAN, Evanston, Ill.

A FAMILY OUTBREAK OF LEAD POISONING FROM THE BURNING OF STORAGE BATTERY CASINGS. J. WYLLIE, Canad. M. A. J. **70**:287-290 (March) 1954.

A family living in a small shack heated by an old cooking stove used storage battery casings for fuel. Three of the family had no complaints, one boy died of encephalopathy, another boy had colic, and the mother had lead line in the gums and weakness in the right grasp so that Teleky's sign was easily demonstrated. Attention is called to the importance of the respiratory tract as a portal of entry for lead. Signs of toxicity develop more quickly than when 10 times as much lead is swallowed.

MCGUIGAN, Evanston, Ill.

Books

The Encyclopedia of Child Care and Guidance. Edited by Sidonie M. Gruenberg. Price, $7.50. Pp. 1016, with 123 illustrations. Doubleday & Company, Inc., Garden City, N. Y., 1954.

This amazing compendium of information was conceived and written for teachers, social workers, nurses, ministers, and guidance counselors, but most of all for intelligent parents who would like an authoritative guide for child care. Physicians would find it a rapid reference of bona fide information upon which they may rely, and in a brief and concise form.

The book is divided into two sections. Part I is a detailed guide to child care and guidance, containing more than 1000 entries arranged alphabetically and including all information relative to child care from "Acne" to "Youth Organizations," there apparently being no data in the "Z" category. All of this material is completely cross indexed, which markedly increases its value. Part II is made up of 30 chapters on basic aspects of child development and guidance, written by leading authorities in the field. Anyone wanting quick and specific suggestions on particular problems will find them easily in Part I. The reader who wishes a broader picture may find at the end of each item references to related topics and chapters in Part II. In the cross references even the casual reader will note the organic unity and sense of interrelatedness underlying the editor's approach to children and the world in which they grow up. The sketches are simple and refreshingly illustrative of the topics to which they refer.

It is difficult to appraise critically the authentic content of this prodigious book in a short review. It has been the custom of this reviewer to read completely any literary effort before giving an honest opinion. The voluminous nature of the vast amount of material enclosed between the covers of this encyclopedic tome precludes this wish, but by a careful inspection of the table of contents, by an evaluation of the contributors, and by sectional reading of the text—all impress one that this book does fill a definite need.

Every serious-minded pediatrician in his daily practice senses the inadequacy of many earnest parents who desire to do their jobs of parenthood better than their limited scope in this field would permit. We live in an authoritative age, where parents have been conditioned to seek written dogma and rules for their actions and viewpoints. The effects of advanced schooling, professional training, and modern business efficiency may lead many modern parents to adapt a mechanical perspective of their children and to search for a concise manual of instructions to aid them in their task. Too often this desire for specific authoritative aid will be adequate as long as the child follows the book, but can be most damaging to a young individualist and to his parents as well. If the child fails to respond to his theoretical requirements, the suspicion may arise that he is defective in some way.

This book fills the requirement of orienting the truth-seeking parents in their quests for sound information. Here is a reference manual which presents to such parents the views of accepted modern authorities in child rearing in a concise and palatable form. It is a book to be recommended to parents by the pediatrician for specific help and as a sound approach to their problems. It is also an excellent handbook of reference to all those, other than parents, who are interested in or who deal with children, both by presenting elementary views and by giving an invitation to enlarge their horizon to broader vistas in this field of instruction. It also may serve as a guidon for the better-equipped reader who is desirous for a more detailed knowledge of the subject. This book supplies these various needs of those who wish to be informed in all of the approaches to modern child culture, and it is commended to its readers.

Deprived Children: A Social and Clinical Study. By Hilda Lewis, M.D., M.R.C.P. Price, 9 shillings 6 pence. Pp. 163, with no illustrations. Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, 1954.

When a child is removed, by law, from his parents or his home for whatever cause—neglect, desertion, delinquency, etc.—there is the feeling that the child should have a thorough social and psychological study in order that his future treatment will be in line with his individual needs. During the war years the Mersham Reception Centre was a place in England where children were remanded by the Kent County Council for study before being sent to their homes.

The time spent at the Centre, usually from three to six weeks, gave the staff an opportunity to study the child and to make recommendations for the best type of home.

The Centre continued in operation from 1944 to 1951, during which time 500 children were admitted. After the closing of the Centre, the committee in charge decided that valuable information could be obtained by studying the records for the seven operating years and the present condition of the children who had been placed in homes after their stay in the Centre.

All the children investigated had been in their present homes two or more years. This work was delegated to Dr. Hilda Lewis, the psychiatrist at the Centre, and the book, "Deprived Children," is the result.

The first four chapters deal with the make-up and work of the Centre, the types of children admitted, the family background of the children, personality and patterns of behavior, influence of family and environment on behavior, and, especially, the reactions of children when separated from their parents. The fifth chapter tells of the follow-up. Of the 500 admitted, 240 were interviewed either by a personal visit or by a letter.

The proportion of children in good psychological and social condition had doubled during the two or more years since the children were at the Centre. There was improvement in 63%, no change in 29%, and 8% were worse. Neurotic symptoms were more persistent than delinquent behavior. The child who had been placed so he had contact with his parents or relatives showed the better results. The child separated from his mother before 5 years of age had less chance of favorable outcome.

The most enlightening part of the book is Dr. Lewis' "General Reflections." She brings out forcefully that there is no suitable substitute for parental love for children and that one should be very hesitant about separating children from their parents if there is any chance that the family can be kept together.

Ciba Foundation Symposium on Hypertension: Humoral and Neurogenic Factors. Edited by G. E. W. Wolstenholme and Margaret P. Cameron, assisted by Joan Etherington. Price, $6.75. Pp. 294, with 73 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1954.

This book is the record of another Ciba symposium which took place in London, in July, 1953. Among the points discussed are reflex blood pressure regulation, the secretion of norepinephrine by the arterial wall, 5-hydroxytryptamine, vasoconstrictor substances, and hexamethonium.

The laboratory diagnosis of pheochromocytoma is reviewed. The occurrence of a significant number of false-positive piperoxan (benzodioxan) and phentolamine (Regitine) tests suggests the use of the more reliable quantitative determination of the amount of epinephrine and norepinephrine in the urine. An additional advantage of the latter is the continued increased excretion of these hormones during normotensive intervals.

Studies on experimental production of hypertension in the rat are particularly interesting. For several days after being made ischemic, the kidney secretes a renal pressor substance; after this period of time the hypertension is maintained by an extrarenal pressor mechanism. This latter phase emerges because the contralateral kidney becomes altered by the initial period of hypertension and is no longer able to inhibit the extrarenal pressor mechanism. A permanent alteration of the "good" kidney occurs after several weeks, so that removal of the ischemic kidney at this later time would result in no relief from the hypertension.

The relationship between hypertension and electrolyte and water balance is discussed. Marked sodium restriction results in a fall to normal levels of the blood pressure of the majority of cases so treated. It is significant that no change in corticosteroid excretion occurs. In experimental hypertension—no matter how it is produced—there is a retention of salt and water. Furthermore, it is shown that the molecule sodium chloride is directly related to the hypertensive state in patients and that administration of either ion without the other does not raise the blood pressure of a temporarily normotensive, salt-restricted, hypertensive individual.

Of interest is a presentation of several patients in whom signs of progressive hypertensive disease appeared despite the presence of a normal blood pressure.

Altogether, we are presented with a great deal of extremely valuable information of special interest to investigators in this field.

Ciba Foundation Symposium on The Kidney. Edited by G. E. W. Wolstenholme. Price, $6.75. Pp. 333, with 125 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1954.

Five years ago Ciba, international pharmaceutical manufacturers, established in London a foundation having as its basic purpose the provision of a meeting place where scientists from all over the world could exchange ideas. In this spirit 35 eminent European and American researchers in the fields of the kidney and electrolyte metabolism met in July, 1953. This volume is a complete record of that meeting.

The symposium is concerned with five general topics. These are listed below along with a few of the very many points of interest.

1. Structural and functional relationships in the kidney. The demonstration that the osmolarity of the contents of adjacent tubules and blood vessels is the same and that this osmolarity is normal in the cortex and high in the medulla of a kidney excreting a hypertonic urine forms the basis of a theoretical "hair-pin counter-current system" and provides one of the most interesting and controversial discussions of the meeting.

2. Tubular functions other than the regulation of acid-base balance. It is demonstrated that the $Tm_{glucose}$ is actually a mean value; from this it is postulated that there is a minimal Tm_G at which point the least efficient nephrons will begin to spill glucose, and a maximal Tm_G at which the most efficient reabsorbers will finally begin to spill. In nephrotoxic states as well as in one of the two types of renal glycosuria, a decrease in the Tm_G results from an unequal decrease in the glucose-reabsorbing efficiency of the already unequally efficient members of the nephron population.

3. Renal share in the regulation of acid-base balance. It is theorized that sodium reabsorption is the only mechanism involving energy-utilizing, active transport. To replace this sodium taken from the tubule lumen, there is a competition between hydrogen and potassium, the intracellular pH and potassium content being the determining factors.

4. General problems of electrolyte excretion. Postoperatively, water retention (independent of sodium retention) for approximately one and one-half days occurs as a result of an increase in circulating adrenal hormone. During the first postoperative day sodium retention, accompanied by increased potassium excretion (suggesting adrenal hormone influence), also takes place. On the third or fourth postoperative day sodium retention again occurs, this time without a necessary increase in potassium excretion.

5. Renal share in volume control of body fluid. Studies on anuric subjects reveal an increase in the total body water along with a decrease in the extracellular fluid. It is pointed out that in metabolizing body stores as well as food, water is produced, especially from fats. Therefore, it is suggested that fats not be given to anurics and that their water intake be less than their insensible loss. Furthermore, hypertonic saline may have to be given to maintain the "effective osmotic pressure" (total osmotic pressure minus that of urea) of the extracellular fluid in order to prevent absorption of water into the cells and subsequent water intoxication. However, should the patient be overhydrated, hypertonic saline administration is dangerous and some form of extrarenal dialysis is suggested.

This symposium well serves its basic purpose and is recommended particularly to those involved in investigative work in these fields.

Problems of Infancy and Childhood: Transactions of the Seventh Conference, March 23 & 24, 1953. Edited by Milton J. E. Senn. Price, $2.75. Pp. 196. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York 36, 1954.

Five presentations on different aspects of the psychological development of infants and children are included in this monograph, which appears in the same form as previous transactions of the Josiah Macy Jr., Foundation.

Dr. Emmy Sylvester presented a pediatrician's clinical observations of the undesirable effects of mechanized child-rearing practices without realistically appraising and meeting the individual needs of children. Overpermissiveness, overindulgence, and the tendency to theoretical generalizations by those who give advice regarding child-rearing practices to parents were particularly condemned.

Dr. John Bowlby, a psychiatrist from England, presented the results of systematic observations on the effect of separation of children between 1 and 3 years of age. This study resulted in the production of the film, "A Two Year Old Goes to the Hospital." The ability of infants and

very young children to use their resources as autoerotic behavior, play activity, and relationships with hospital personnel to maintain an emotional homeostasis in a period of psychological stress were discussed. Several of the discussants presented evidence of the variability of the reaction of different children to separation from home.

Dr. Gerald Caplan, a child psychiatrist formerly of Israel, presented an interesting review of 25 years of practice of infant and child rearing in communal settlements in Israel. Infants and children are cared for by professional workers in nurseries and child centers from birth. This movement was begun because of the lack of confidence of parents in their own emotional adequacy. To insure the mental health of their children, they hired professional child workers to assume the responsibility of the child's care and training. The parents could see the children for a few hours in the evening and on weekends. With this dilution of the child-parent relationship, group identification was fostered. Though boys and girls lived together through their adolescence in a relatively permissive atmosphere, sexual morality developed, as in a family, to the extent that members of the same Kibbutz (as the units for the older children were called) never marry. The emotional stability of adults raised in the Kibbutzim was discussed.

In the report of the Subcommittee on Rooming-In, the film "Physiologic or Natural Childbirth" is reviewed and an excellent discussion of newborn and infant feeding, rooming-in, and infant care is presented. The liberalized attitudes of some obstetrical services regarding visiting by members of the mother's family was particularly refreshing. This discussion included contributions of well-known people from many disciplines concerned with practical problems with the rooming-in practice. This report is an excellent summary of modern concepts of neonatal care in America and is a suitable finale to the last of the Josiah Macy Jr. Foundation conferences.

Growth and Development of Children. By Ernest H. Watson and George H. Lowry. Price, $7. Pp. 296, with 70 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

The subject of growth and development in recent years has become basic to students of pediatrics. It has become of paramount importance to those candidates preparing for American Board of Pediatrics and other examinations. Surely a fundamental knowledge of the processes of development and growth is essential before an understanding of the abnormal can be appreciated. To this end there are several good books available which cover the subject, and the present volume here discussed is one of the best of these. An index of its reception by students and their preceptors lies in the fact that a new edition has been required within three years of the publication of the first one.

In comparing the original with the new edition, the word "reprinting" would be more apropos. There has been added a new chapter on "Facial Growth and Dentition," of 20 pages, which was previously covered in 3 pages under the section of "Organ Development." Several new subheadings have been added, such as "Growth and Development of the Legs and Feet"; "Basic Needs of Every Child," and an amplification of the section on "The Skeleton." There are also several new charts and graphs which help to clarify some of the data for the reader. These additions enlarge the book from 260 pages to 296 pages. Otherwise, the new "edition" is generally the same as the first, and anyone having the original issue will find little difference between the two printings.

If this new issue represents new material as well as amendments and revisions, as the preface states, then it is amiss that the authors have not seen it of import to enlarge on the discussion of "Basal Metabolism." The procedure of measuring the metabolic rate of infants and children has always been fraught with technical difficulties and variable interpretations, so that any new method of obtaining similar information would be most welcome. With the development of the technique of estimating the radioactive iodine uptake of the thyroid gland and the method of calculating the serum protein-bound iodine, two new procedures are available which greatly facilitate the study of normal and pathologic functions of the thyroid and other endocrine organs. These two new techniques are both mentioned by name in the chapter on "The Role of the Endocrine Glands," but are not discussed in the section given over to "Basal Metabolism." These newer tests are now generally available in most hospitals and many private and clinical laboratories and should have a special discussion and emphasis in a book so new and complete as the one under discussion.

The use of eponyms in the naming of diseases and syndromes is continued in this book, when the general tendency at present is to substitute chemical and descriptive names. There seems to be no consistency toward listing disease entities in the index, such as Hurler's disease, Morquio's

disease, or von Gierke's disease, while Niemann-Pick's disease, the McCune-Albright syndrome, and Fröhlich's syndrome are correctly indexed. It is not quite clear why this discrimination is made unless ascribed to an idiosyncrasy of the indexer. The accurate listing of proper names and all other units of data should be the duties of the authors and not left to the vagaries of the professional indexer.

Many readers may object in this otherwise erudite classic to the appearance of a form of grammatical error which offends some readers. The expressions "the test shows" and "growth demonstrates" are incorrect because an inanimate subject can not have an active verb. These and other similar "cliches" have been handed down from one generation of medical authors and students to another. It may be accepted by some that usage popularizes a given phrase, but these "hybrids" have no place in a work the very nature of which implies accuracy and detail, as in an effort of the type here discussed.

This book remains a worthy contribution to the pediatric literature and is recommended to those who are interested in the fundamental subject of growth and development.

Essentials of Pediatrics. Edition 5. By Philip C. Jeans, F. Howell Wright, and Florence G. Blake. Price, $4.75. Pp. 808, with 100 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1954.

This book has been generally accepted as the standard text in pediatrics for nurses, and it has had the respect of both nursing and pediatric authorities in this field for years. Evidence of its preeminence in nursing pediatrics lies in the fact that the recent edition is the fifth in 20 years. With the passing of Dr. Philip Jeans, who has been the chief author, Dr. F. Howell Wright, Professor of Pediatrics at the University of Chicago, replaces him as the medical editor. Miss Florence Blake, also of the University of Chicago, remains as the associate editor.

Many changes in the content are apparent when one compares the present with the immediately previous edition, the material having been extended from 627 to 808 pages. The section on growth and development has been completely revised, involving the addition of 20 more pages, as has the section on general nursing care, including the significant insertion of "Nurse-Parent Relationship." To this latter unit also has been added a new section on pediatric therapy, with a discussion of fluid administration, replacement (blood) therapy, and the newer variants, including chemotherapy, corticotropin (ACTH) and cortisone administration. Many new additions and revsions have been made in the sections pertaining to the diseases of the systems, bringing them up to modern concepts. The sections on viral, bacterial, and mycotic infections have been completely revised in keeping with the newer knowledge in these specific fields.

It is noted with interest and some warm affection toward the new editorial policy that the sections on nutrition and nutritional diseases remain almost unchanged—a compliment to Dr. Jeans, whose preeminence in this field could not be excelled. The glossary in the new edition is dispensed with, and instead, the unusual and technical terms are defined in the table of contents or at the place in the text where they occur. The bibliography is appended to each chapter rather than at the end of the book, which is a commendable innovation.

As a text of this type gradually evolves with advancements in learning, one is impressed by the voluminous amount of information (808 pages) which must be encompassed by a student nurse in the instruction in only one of the specialties and with the fact ever in mind that the average neophyte in nursing comes to his or her training with only a high school preparation. The material presented in this book is prodigious and encyclopedic, so that by evolution, a simple text in pediatrics can easily become a comprehensive reference work of graduate level. It is hoped that this constant and traditional text for instructing nurses in the essentials of pediatrics does not fall prey to its own weight of detail.

It is also hoped that the present authors do not forsake the simple and direct mode of writing of the original author-editor. Dr. Jeans was a master of English composition and expression. His style is classic and puristic, and this is one of the reasons why all of his books and articles have remained as exemplary pieces of expository writing. He frowned on impurities of expression and has always kept his material free of the common cliches and "scientific doggerel" which have penetrated medical composition in recent years. It may be expected that this technique of facile expression will constantly continue to flavor the future editions of his books.

This text will remain the leading one of its kind as a guidon for nurses in pediatrics, and it is highly recommended to nursing school administrators and teachers for many future generations of nursing students.

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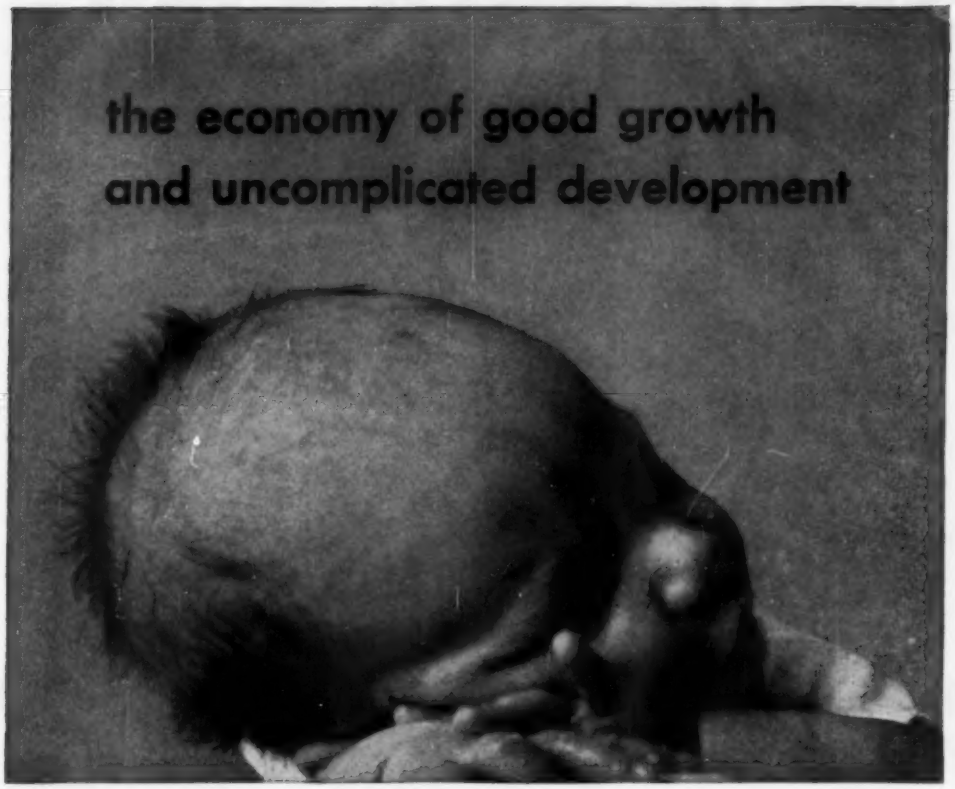

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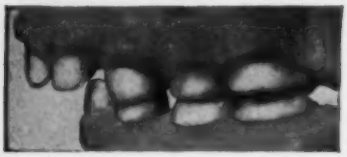

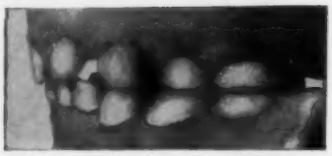

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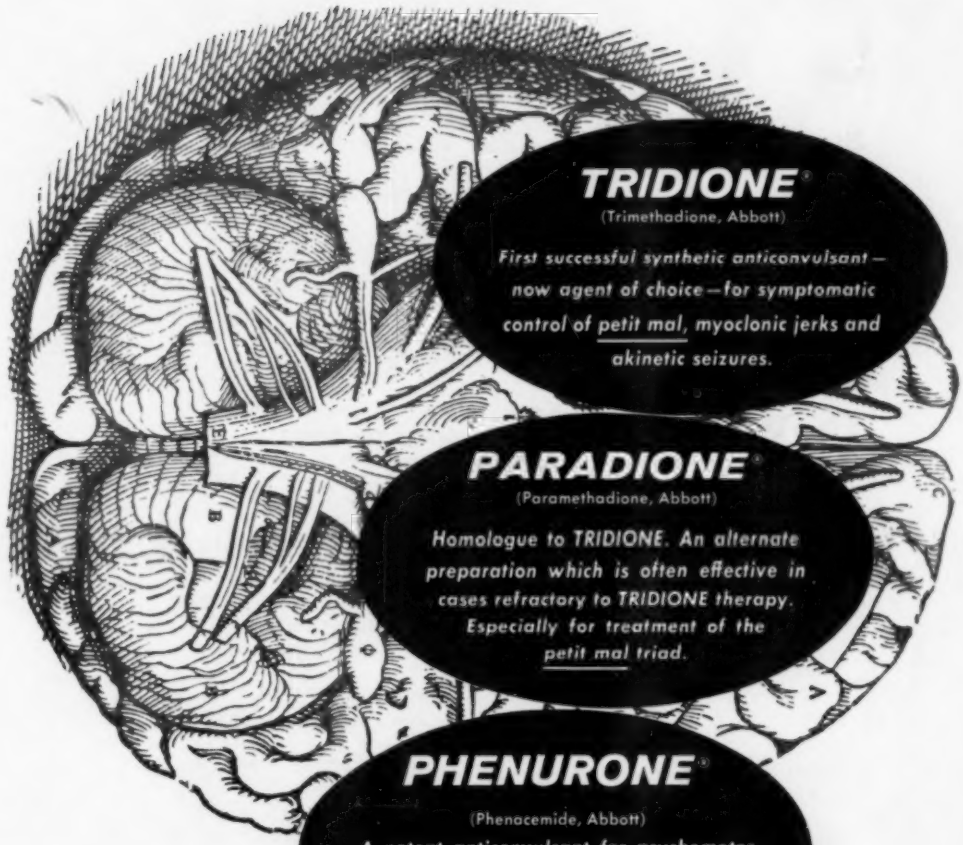

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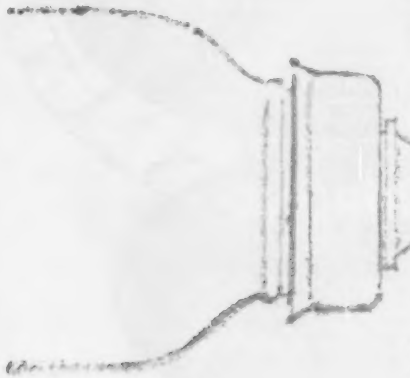

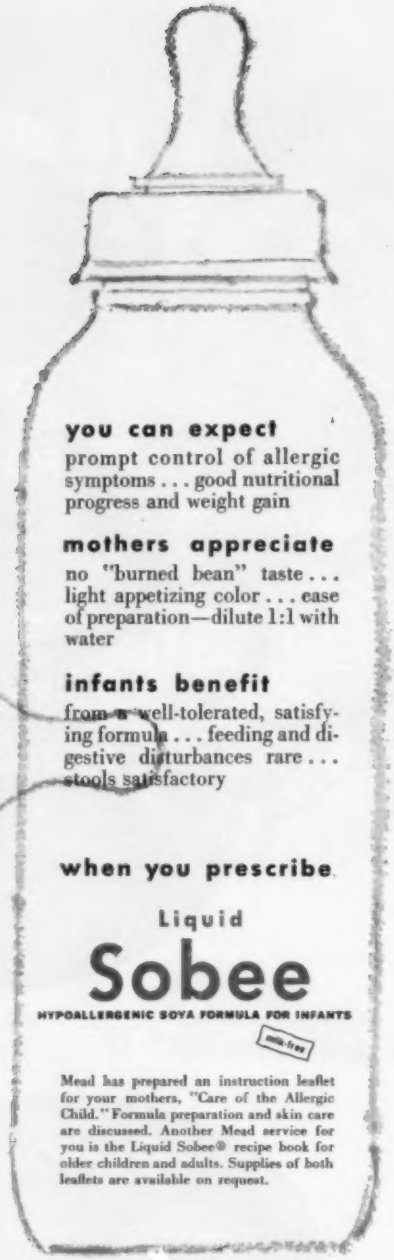

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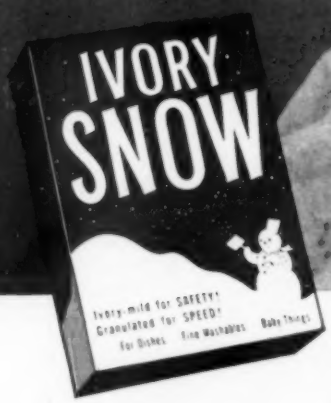

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